

Through the Looking Glass: I. Why Cross-Fertilize?

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Front Matter

About

The following pages represent the first volume of a book. The main goal was to introduce the evolutionary problem of sexual reproduction, with a focus on competition between sexual and asexual females. But I also incorporated some ideas on genetic polymorphism and phenotypic plasticity with the goal of exploring “variation strategies” more generally. Finally, I tried to weave in some history of the field, along with some philosophy of science.

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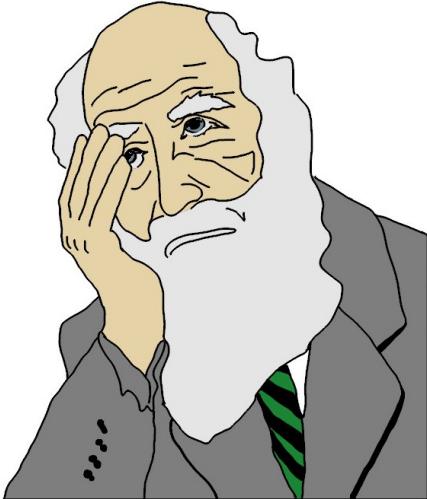
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Chapter 1

Why Sex?



1.1 The Question

Most PhD programs require that students pass a preliminary examination. This was certainly true in my case. I was a PhD student at the University of Arizona studying rocky intertidal communities in the Northern Gulf of California. But the exams were not focused on our research. They were “depth-of-knowledge” exams. My question from Professor Astrid Kodric-Brown instructed me to read the preface of G.C. Williams’ book, *Sex and Evolution*, which contains the following text (1975): “This book is written from a conviction that the prevalence of sexual reproduction in higher plants and animals is inconsistent with current evolutionary theory.... Many well informed readers may disagree with much of my reasoning, but I hope to at least convince them that here is a crisis at hand in evolutionary biology.”

The question was something like this: “Why does Williams think that sexual reproduction poses a crisis for evolutionary biology, and what is the solution?” A crisis? That was news to me. How could there be a crisis in evolutionary biology 40+ years after the modern synthesis? My graduate course in theoretical population genetics did not mention any crises. I was not convinced. And a little freaked out.

The structure of our exams was very loose. I don’t remember having a deadline to produce a written answer, but I do remember that I spent several months on just this one question. During much of this time, I was doing field work in Sonora, Mexico, sometimes under very harsh conditions. But the more I studied the question, the more fascinated I became. I came to think that there was, indeed, a very real anomaly presented by sexual reproduction. Williams was right. Perhaps I was especially interested in this anomaly because I had read Thomas Kuhn’s *The Structure of Scientific Revolutions* as an undergraduate (1970). Kuhn made the case that dissecting anomalies can lead to interesting advances and that made sense to me. While I eventually produced an essay to address the question, the answer felt incomplete. I wanted to know more. There were many hypotheses, but there was no clear general explanation. Many years later, I am still working on my prelim question. This book is my revised answer.

1.2 The Problem

There are many problems with sexual reproduction, including the time spent finding mates and the risk of contracting sexually transmitted disease (review in Lehtonen *et al.* 2012). However, while important, these costs do not form the core of the paradox. Historically, the paradox of sex stems from two things: (1) the cost of meiosis, and (2) the cost of producing males.

1.2.1 The cost of meiosis: reduced relatedness

The “cost of meiosis” was proposed by George Williams (1975). His idea was simply that females are only half as related to their outcrossed offspring as they are to their self-fertilized or parthenogenetic offspring.¹ (See [Glossary](#) for condensed definitions.) Williams’ idea also had theoretical support, as R.A. Fisher had already shown that an allele causing self-fertilization would rapidly spread to fixation, barring severe inbreeding depression (1941). So, why cross-fertilize? The persistence of cross-fertilization despite the cost of meiosis formed a paradox. This paradox created the crisis that Williams saw in evolutionary biology.

1.2.2 The cost of males

The other way to look at the problem was proposed by John Maynard Smith (1971, 1978). Here the issue is not relatedness. The problem stems rather from the difference between sexuals and asexuals in their per-capita birth rates (Figure 1.1). Imagine a population of sexual individuals at carrying capacity (K_{sex}). At K_{sex} the sexual females are, by definition, simply replacing themselves. This means that each sexual female is, on average, producing one son and one daughter. Both sons

¹It is not meiosis *per se* that is costly. As Williams realized, the cost stems from the reduction in relatedness between parent and outcrossed offspring. Indeed, in a later paper, Williams (1975) refers to the cost of meiosis as the “paradox of kin selection.” Why should organisms invest resources in kin with a relatively low level of relatedness, r (outcrossed progeny: $r = 0.5$), rather than in self-fertilized kin with a high level of relatedness ($r = 1$)? (See Dagg 2016.)

and daughters contribute genetically to the next generation, but only females give birth. Now, consider a mutation in a single female that causes her to reproduce asexually. She gives birth to two daughters instead of one daughter and one son. These two asexually produced daughters both give birth to two more daughters. Hence, after just two generations, the asexual female has four granddaughters, while the average sexual female has just one granddaughter (Figure 1.1). This asymmetry should lead to the rapid replacement of sexual females by asexual females (Figure 1.2). And by “rapid,” I mean within tens of generations, even for very large populations (Lively 1996). We thus seek a selective force that can give an advantage to sexual reproduction on a very short time scale.

Several assumptions went into Maynard Smith’s model for the cost of males. In particular, he assumed that sexual females and asexual females make the same number of offspring, and that the survivorship of these offspring is also the same. Maynard Smith referred to this as the “all-else-equal assumption.” Unfortunately, some authors have taken the phrase “all-else-equal” to mean that everything else is exactly equal. But this is not the case. Maynard Smith did not assume, for example, that sexuals and asexuals have the same ploidy value.² His model only assumes that sexual and asexual females have equal fecundities and survivorship probabilities (see Section 1.4). Under this assumption, a very rare clone would double in frequency in the next generation. Maynard Smith called this doubling-when-rare the two-fold cost of sex.

1.2.3 Contrasting the costs

The two alternative costs of sex raise an immediate question. Does the cost of sex result from reduced relatedness between mother and offspring, or from the cost of producing males? Or is the cost some combination of both? These questions are not easy to answer; but there is an algebraic solution, which suggests that the (1) two costs are mutually exclusive and (2) that they apply to different kinds of uniparental progeny (Lively & Lloyd 1990). Roughly speaking, I think we can adopt the following rules for the purpose of this book. When considering the spread of a rare allele that induces self-fertilization in hermaphrodites, the appropriate cost is Williams’ cost of meiosis. Here we have a single population in which the selfing allele is under positive selection because it has a transmission advantage. On the other hand, when we consider the spread of a clone into an obligately sexual population, we are dealing with competition between two different reproductively isolated groups. One group (the sexuals) produces males, which do not make offspring. The other group (asexuals) produces only females. Here the cost of sex stems from producing males. But the two costs do not combine. The cost of sex is not four-fold.

1.2.4 The cost of recombination

There is another paradox of sexual reproduction known as the “cost of recombination.” Here the competition is not between sexual and asexual females, or between outcrossing and selfing alleles, but rather between alleles that modify the rate of recombination. So instead of asking “Why cross-fertilize?” we can assume cross-fertilization and ask, “Why is there excess crossing-over during meiosis?” Here is the paradox. If combinations of alleles at different loci are favored by natural selection (because together they create high-fitness offspring), then recombination would break these favorable allelic combinations apart. So, it makes no obvious sense to recombine more than

²Asexuals are often polyploid versions of their sexual ancestors.

THE COST OF MALES

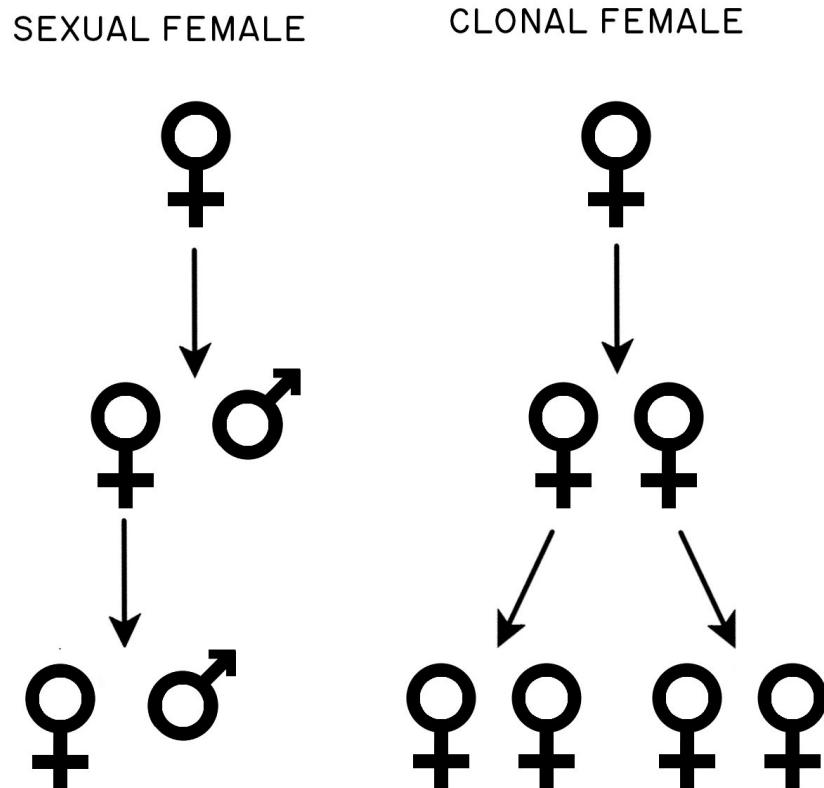


Figure 1.1: The cost of males. Imagine a single clonal female in a sexual population at carrying capacity, K_{sex} . At K_{sex} , the sexual females are, on average, producing one daughter and one son. In contrast, the clonal female produces two daughters and four granddaughters. Hence, the clonal lineage should rapidly eliminate the sexual population (Figure 1.2). However, in nature, asexual reproduction is very rare in both plants (Whitton *et al.* 2008) and animals (Vrijenhoek 1998). Hence the paradox. Why is sexual reproduction so costly and yet so common?

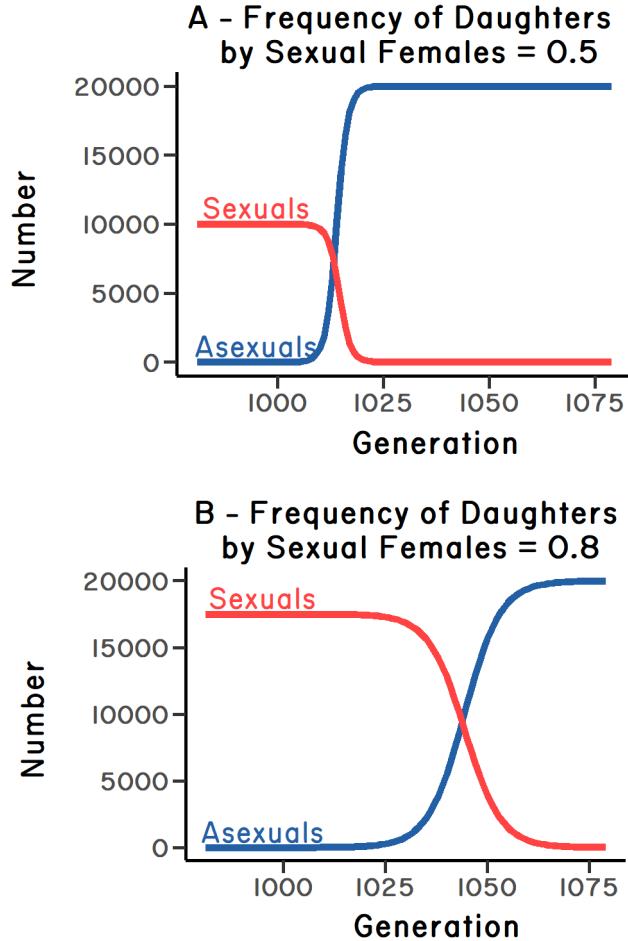


Figure 1.2: Clonal invasion dynamics. Results from a simulation study in which a single clonal individual was introduced into a sexual population (Lively 2009). **A** (top). Results for a 1:1 sex ratio in the sexual population. Here the frequency of daughters produced by sexual females was 1/2. The sexual population was initiated at carrying capacity: $K_{sex} = 10,000$. A single parthenogenetic female was introduced by the simulation at generation 1,000. Note that the asexual lineage replaces the sexual population in about 25 generations, and that it reaches a higher carrying capacity $K_{asex} = 20,000$. **B** (bottom). Results for a female-biased sexual population. Here the frequency of daughters produced by sexual females was 0.8. The sexual population was initiated at carrying capacity: $K_{sex} = 17,500$. As above, a single parthenogenetic female was introduced into the population at generation 1,000. Note that the asexual lineage replaces the sexual population, but it takes longer. The simulation assumes annual reproduction and non-overlapping generations. The R code for the simulation, including interactive graphical output, can be found [here](#). The interactive graph can also be run [here](#) for users without R.

needed for normal meiosis. Indeed, Lewontin (1971) formally showed that “the mean fitness of the population at equilibrium is a maximum in the absence of recombination.”³ Hence, there are two interrelated anomalies: cross-fertilization *per se* and meiotic recombination. Ideally, any theory that explains the persistence of biparental sex could also solve the paradox of recombination. But this need not be the case. They could have different solutions.

1.2.5 Darwin’s view

Even before the cost of males and meiosis were so dramatically revealed by Williams and Maynard Smith, biologists were reckoning with the anomaly of sex (Dagg 2016; reviews in Meirmans 2009). One of the earliest of these biologists was Charles Darwin. After he published the *Origin of Species*, Darwin was doing hand-pollination experiments at Down House on three species of a curious annual plant in the genus *Primula*. The plant is curious in that it has two morphs. One morph has a style that extends beyond the anthers (the long-style morph), and the other morph has anthers that extend beyond the style (the short-style morph). Botanists refer to this condition as distyly (Figure 1.3). Darwin found that crosses between the different morphs of the same species resulted in a very successful production of seeds, but crosses between unrelated individuals of the same morph were dramatically less successful (1862). In discussing these results, Darwin speculated that the two morphs may have evolved to ensure cross-fertilization: “Whether or not the dimorphic condition of the *Primula* has any bearing on other points in natural history, it is valuable as showing how nature strives, if I may so express myself, to favour the sexual union of distinct individuals of the same species.”

Darwin then asks a killer question. Why should the union of elements from distinct individuals be favored? Why, in fact, is there sex? “Nor do we know why nature should thus strive after the intercrossing of distinct individuals. We do not even in the least know the final cause of sexuality; why new beings should be produced by the union of the two sexual elements, instead of by a process of parthenogenesis. The whole subject is as yet hidden in darkness.” Darwin’s question shows that the cross-fertilization is curious, even without considering the costs of sex. It also shows how Darwin was drawn to anomalies on theory.⁴

It is interesting to note that, in Darwin’s quote above, he switches from discussing mechanisms to prevent self-fertilization, such as distyly, to discussing parthenogenesis. Self-fertilization is a sexual process (involving the formation and fusion of gametes from the same parent), while parthenogenesis is an asexual process that does not generally involve meiosis and syngamy (review in Bell 1982). But parthenogenesis and self-fertilization are conceptually related, as they are both uniparental forms of reproduction. Hence, it makes sense that Darwin would switch back and forth between these two different forms of uniparental reproduction. Why cross-fertilize if either selfing or parthenogenesis is an option?

³Lewontin (1971) was following up on Fisher’s (1930) verbal suggestion that selection should act to reduce recombination. For example, Lewontin (1971) writes, “I will show ... that Fisher’s conjecture is indeed correct.” Importantly, in his last paragraph, Lewontin wonders why recombination rates are greater than zero, and he suggests that the answer “must be sought in some more general long-term advantage for adaptation to a varying environment, or else to some mechanical necessity of recombination for the orderly distribution of chromosomes, as suggested by Darlington (1939).” (See also Bell 1982).

⁴For example, Darwin calls the evolution of sterile castes in social insects an “insuperable difficulty” for his theory of evolution by natural selection (pages 236–238 in 1859).

Hand pollination experiment on *Primula*: a contrivance for cross-fertilization?

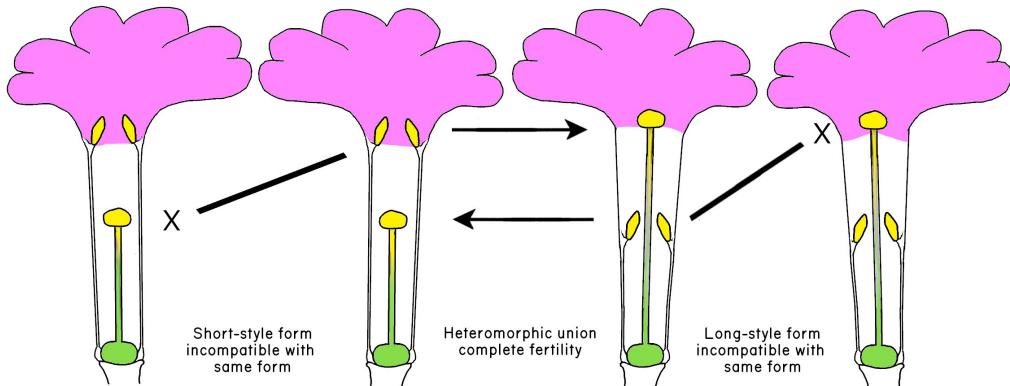


Figure 1.3: Two flower morphs (distyly) in *Primula*. Darwin found that the short-styled morph (left) is incompatible with other short-style morphs and that the long styled morph (right) is incompatible with other long-style morphs. But the two different morphs can cross-fertilize. The arrows show movement of pollen from anthers to stigmas. The “X” indicates incompatibility. Redrawn from Darwin (1862) by ZMD.

There may be another reason why Darwin pivots to parthenogenesis. Just prior to the publication of Darwin's (1862) paper on *Primula*, Carl Theodor Ernst von Siebold (1856) published his observations on the successful development of adults from unfertilized eggs, which he called “parthenogenesis” (virgin birth). These were revolutionary observations, which caught Darwin's attention. In a letter to his mentor, J.S. Henslow, Darwin mentioned von Siebold's discovery as follows: “There is no greater mystery in the whole world, as it seems to me, than the existence of sexes, – more especially since the discovery of Parthenogenesis” (Darwin n.d.).

However, the discovery of parthenogenesis was met with some hostility.⁵ Consider, for example, the following statement by Rudolf Wagner in his 1857 review of von Siebold's book on parthenogenesis (as translated from the original German by Churchill 1979): “I must unfortunately say that one of the most unpleasant of facts, [*Parthenogenesis*] has been introduced into physiology, which for the hope of so-called general laws of animal life-phenomena *is most distasteful*. It is impossible, considering the glorification of our highly vaunted progress in the theoretical understanding of the life processes, for it to be welcomed or particularly encouraged; and sincerely speaking, I can be as little pleased about it as a physicist would be if suddenly one or more exceptions to the law of gravitation were discovered” (Emphasis added).

Clearly, Wagner was not pleased with the discovery of asexual reproduction, calling it unpleasant, unwelcome, and distasteful. By contrast, Darwin did not find the idea to be distasteful in any

⁵The case has been made that Charles Bonnet had discovered asexual reproduction in aphids in 1740 (see Lawrence 2009).

way. He wondered instead why it was not more common. For example, Darwin (1868) wrote, “Parthenogenesis is no longer wonderful; in fact, the wonder is that it should not oftener occur.”⁶

Over 100 years later, W. D. Hamilton (1975) was also pondering the evolution of outcrossing, and he wrote something conceptually similar: “[c]omplete inbreeding abandons the obviously important advantages of sexual reproduction, whatever these are.”

Whatever these are! The advantages of outcrossing were obviously important because cross-fertilization is so dominant. But the source of these advantages was not clear. At about the same time, Maynard Smith (1976) mused, “One gets the feeling that some essential feature of the situation has been overlooked.”

I now think that John Maynard Smith was correct. An essential feature had indeed been overlooked: parasites.

1.3 Summary

1. Obligate sexual reproduction is subject to invasion and replacement by all-female asexual lineages that do not pay the cost of males.
2. Obligate outcrossing in simultaneous hermaphrodites is subject to invasion and replacement by self-fertilization unless inbreeding depression is severe.
3. The exchange of DNA between different parental chromosomes (recombination) is similarly paradoxical.
4. Why then are recombination and cross-fertilization so common?

1.4 Appendix: Maynard Smith’s Model

John Maynard Smith’s (1978) model, reproduced here, shows the cost of producing males.⁷ Let N_{asex} be the number of asexual females at time one, while N_{sex} gives the total number of sexual individuals (males plus females) at time one. Let B_{asex} give the number of offspring produced by asexual females, and S_{asex} gives the survival probability of asexual offspring to maturity. The number of surviving asexual offspring is then $= B_{\text{asex}}S_{\text{asex}}$. Similarly, let B_{sex} be the number of offspring produced by sexual females, and let S_{sex} give the survival probability of sexually produced offspring. Maynard Smith assumed that all individuals reproduce once and then die. Let r be the frequency of females in the sexual population. The number of asexuals and sexuals at time two can then be calculated as in the table below. (Note, we do not assume that the population is at carrying capacity).

⁶I suspect that Darwin uses the phrase “no longer wonderful” to mean “no longer astonishing.” See [“How ‘Wonderful’ Lost Its Sense of Wonder.”](#)

⁷I use slightly different variable names, and I try to simplify JMS’s original model.

Table 1.1: Appendix: Maynard Smith's Model

	Time One	Time Two
N. of asexuals	N_{asex}	$N_{\text{asex}}(S_{\text{asex}}B_{\text{asex}})$
N. of sexuals	N_{sex}	$rN_{\text{sex}}(S_{\text{sex}}B_{\text{sex}})$
Freq. of asexuals	$\frac{N_{\text{asex}}}{N_{\text{asex}}+N_{\text{sex}}}$	$\frac{N_{\text{asex}}(S_{\text{asex}}B_{\text{asex}})}{N_{\text{asex}}(S_{\text{asex}}B_{\text{asex}})+rN_{\text{sex}}(S_{\text{sex}}B_{\text{sex}})}$

The fold increase in frequency of asexuals, F , is the ratio of the frequency of asexuals at time two divided by the frequency of asexuals at time one giving:

$$F = \frac{N_{\text{asex}}(S_{\text{asex}}B_{\text{asex}})}{N_{\text{asex}}(S_{\text{asex}}B_{\text{asex}})+r(N_{\text{sex}}S_{\text{sex}}B_{\text{sex}})}/\frac{N_{\text{asex}}}{N_{\text{asex}}+N_{\text{sex}}}$$

Under the all-equal assumption, $S_{\text{asex}} = S_{\text{sex}}$ and $B_{\text{asex}} = B_{\text{sex}}$, giving:

$$F = \frac{N_{\text{asex}}}{N_{\text{asex}}+rN_{\text{sex}}}/\frac{N_{\text{asex}}}{N_{\text{asex}}+N_{\text{sex}}}$$

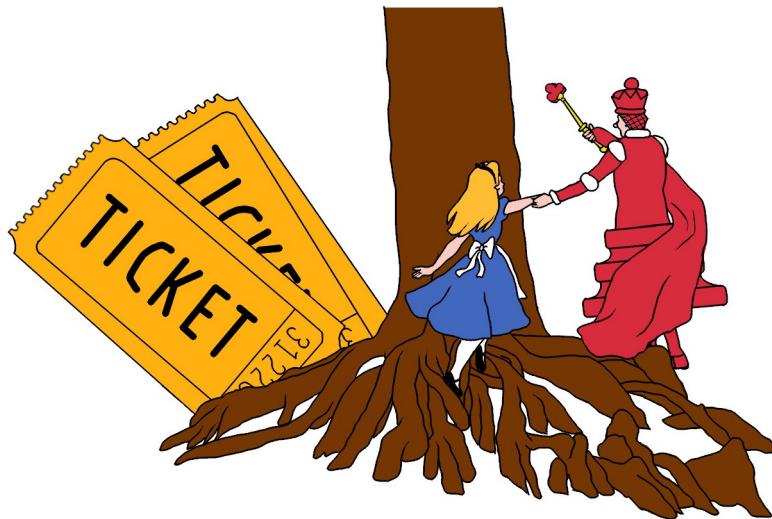
Assuming that there is a single asexual female at time one, we get

$$F = \frac{1}{1+rN_{\text{sex}}}/\frac{1}{1+N_{\text{sex}}} = \frac{1+N_{\text{sex}}}{1+rN_{\text{sex}}}$$

If N_{sex} is very large, the solution reduces to $F \approx 1/r$. Hence, the fold increase in the frequency of asexuals, F , is inversely related to the frequency of females (r) in the sexual subpopulation. Assuming a 1:1 sex ratio, $r = 0.5$. Hence, for an equal sex ratio, the increase in asexuals is \approx two-fold. This result gives the two-fold cost of males. Assuming “all-equal” a clone will double when rare when introduced into a large sexual population.

Chapter 2

The Ecological Hypotheses



The sex/recombination (“sex/rec”) anomaly has attracted some of the best theoretical biologists over the last 50 years leading to at least two dozen hypotheses to explain selection for recombination and/or the persistence of obligate sexual reproduction in natural populations (Kondrashov 1993). In what follows, I first focus on the ecological hypotheses. The ideas underlying these hypotheses provide a handle for understanding some of the foundational concepts in evolutionary ecology.

2.1 The Lottery Model

As part of his book on the evolution of sex, Williams (1975) suggests that sex could be favored in fluctuating abiotic environments. The idea is intuitive: cross-fertilization generates variation among offspring. Hence, in fluctuating environments, sex could increase the probability that some offspring might survive. Williams likens the idea to a unique kind of lottery. For example, he

writes, “Suppose you were offered this choice in a lottery: either you could have several different tickets, or you could have the same number of copies of the same ticket” (p. 15). If you choose N copies of the same ticket (asex) and your ticket wins, you get N times the reward. If you choose N different tickets (sex), you increase the probability of winning something, but the reward is smaller. Williams refers to the idea as the aphid-rotifer model, but the idea has since come to be known as the Lottery Model (following Bell 1982), which is a more descriptive phrase.¹

In my evolution course, I ask a form of Williams’ question but with a slight twist:

If you had a garden, upon which your descendants will depend for many generations to come, would you

1. plant a genetically variable crop, or
2. a monoculture with a two-fold higher yield?

Keep in mind that your descendants will follow your choice.

Often the students rightfully want some clarification. They ask, for example, “Can we use pesticides?” But every time, most students choose the variable crop. I remind them that selecting the variable crop will reduce their yield by one half. They don’t budge. I re-ask the question, doubling the relative yield for the monoculture from two-fold to four-fold. Then to 10-fold. Occasionally, one of the more risk-prone students will select the 10-fold higher yield, but most do not budge. They want genetic variation. I ask them why. Invariably, they say that the environment is going to change. They want to hedge their bets against an uncertain future.

Indeed, Williams’ Lottery Model is about bet hedging. The gist of bet hedging in evolutionary theory is that selection can act to reduce the variance in reproductive success over time, even if it also reduces the arithmetic mean across years (review in Philippi & Seger 1989). Suppose, for example, that we have data for both a monoculture and a genetically variable polyculture (Table 2.1). Let’s assume that the variation in yield is driven by annual variation in abiotic factors such as temperature or precipitation. The effect of planting a polyculture (bet-hedging) can be estimated from the geometric mean, which incorporates the variation in yield over time.

In this example, we find that the monoculture has an arithmetic mean of 240, while the polyculture has an arithmetic mean of only 220. So, I might be inclined to plant the monoculture. However, the among-year variance is very high for the monoculture (relative to the polyculture), driven in large part by the low yields in years 4 and 5. By contrast, the geometric mean for the monoculture is 184, while the geometric mean for the polyculture is 219. Based on this, I might be inclined to plant the polyculture, as it reduces the cost of very low yield in bad years. I think the students see this intuitively. Over the long term, it is better to be risk-averse and plant the genetically variable polyculture. What if, for example, the monoculture produced no food in the last year? The geometric mean would be zero. That would be catastrophic.

¹See Bell (1982) for a deeper historical view of the Lottery Model, which involves contributions by Maynard Smith and others, including Williams. I have tried to distill it down to a simple bet-hedging model here. The original formulation is more complex.

Table 2.1: Bet Hedging

Year	Monoculture	Polyculture
1	350	250
2	400	250
3	300	200
4	100	200
5	50	200
Arithmetic mean	240	220
Variance²	19400	600
Geometric mean (GM)³	184	219
Approximate GM	200	219

The effect of variance on the geometric mean (GM) can be seen by an approximation (Stearns 2000):

$$GM \approx \bar{x} - \frac{\text{var}(x)}{2\bar{x}}$$

where \bar{x} is the mean, and $\text{var}(x)$ is the variance in x . Note that the approximation is equal to the arithmetic mean when the variance in x is zero. Note too that the geometric mean increases as the variance in x decreases. So, if selection operates to reduce the among-year variance in fitness, the outcome of selection will be reflected by an increase in the geometric mean. In general, evolutionary biologists use the geometric mean (rather than the arithmetic mean) to measure fitness over time.⁴

Can sex be favored in variable environments as a bet-hedging strategy? It seems like a very sensible idea provided that the production of genetically variable progeny reduces the among-year variance in offspring survival. But remember, under a two-fold cost of sex, asexuals can replace large populations of sexuals in tens of generations (see Chapter 1). So, if the Lottery Model is correct, significant environmental change must occur very rapidly. The many thousands of years between ice ages, for example, would be too long.

2.2 The Tangled Bank / Frozen Niche-Variation Model

Roughly speaking, the Lottery Model concerns the value of producing diverse offspring in a temporally variable abiotic environment. A different kind of model instead concerns the role of competi-

²The variance in x is equal to the average of the squared deviations from the mean: $\text{var}(x) = \frac{1}{N} \sum_{i=1}^N (x_i - \bar{x})^2$

³The geometric mean is the N^{th} root of the product of N observations. Compared to the arithmetic mean, the geometric mean gives more weight to small values.

⁴The bet-hedging idea dates to Daniel Bernoulli, a mathematical physicist, writing in 1738. Steve Stearns provides an important, fascinating review of how evolutionary biologists (beginning with Cohen 1966) and economists have borrowed from Bernoulli's conceptual framework (2000).

tion for different resource types that vary in space. Let us first consider the Frozen Niche-Variation Hypothesis of Robert Vrijenhoek. The key idea is that the clonal derivatives of sexual ancestors “freeze” some of the genetic variation in the sexual population. This frozen genotype then determines the resource niche of the clone. It seems reasonable to assume that the niche width of a single clone would be relatively narrow compared to the niche width of the genetically diverse sexual population. So, under this idea, a clone could invade a sexual population and perhaps displace it from one of its many niches. But a single clone could not completely replace the sexual population (Vrijenhoek 1979). This kind of process could explain those situations in which sexual and asexual females coexist, which was a major advance.⁵

A conceptually similar model was independently developed by Graham Bell: the Tangled Bank Hypothesis (1982). Bell nabbed the name from the last paragraph of the *Origin of Species*, in which Darwin imagines life as an “entangled bank” of species interacting in a complex network. The core of the idea can be traced back to Howard Levene’s (1953) pioneering model, which showed that polymorphism could be maintained in a spatially heterogeneous environment provided that different genotypes specialize on different resources. Levene’s model was a major advance, as it showed that genetic diversity could be maintained without heterozygote advantage (Section 2.5). This was also one of the first models to fuse population genetics with ecology. But how does multiple niche polymorphism apply to sex? The idea is that if selection results in polymorphism, then a genetically diverse sexual population might be resistant to replacement by a clonal lineage that specializes on only one of the available resource types (as also in the Frozen Niche-Variation Model).

Here is how I pose the Tangled Bank idea to my undergraduate students. I start by giving them a choice between two hypothetical resources, which occur in different parts of the room. One is pizza, the other is broccoli. They all choose pizza. The problem, of course, is that the per-person value of the pizza resource declines as the pizza-eating population grows. At some point, there will be an advantage to specializing on broccoli. This could lead to a polymorphic population composed of obligate pizza eaters and obligate broccoli eaters, where (at equilibrium) the value of both resources is the same. Hence, selection for or against a particular strategy depends on the frequency of that strategy in the population. Perhaps this kind of “frequency-dependent selection” could favor sexual reproduction as a way to diversify offspring in environments where different resource types are patchily distributed in space. This reasoning forms the essence of the Tangled Bank Hypothesis.

One especially interesting aspect of the Tangled Bank Model is that the strength of frequency-dependent selection depends on population density. For example, there would be no selection to utilize the resource of lower value (broccoli) if there were no competition for pizza. This kind of selection, where the advantage to being rare depends on population density, is sometimes referred to as “soft” selection (Wallace 1975).⁶ In other words, soft selection is selection that is both frequency-dependent and density-dependent. This idea contrasts nicely with the Lottery Model,

⁵Vrijenhoek studied the coexistence of sexual fish with multiple clonal genotypes of asexual congeners in natural populations. He mainly envisioned the Frozen Niche Hypothesis as a model to explain the coexistence of multiple clones, but it can also explain the coexistence of sexual and asexual modes of reproduction if clonal diversity is low, and the clones do not compete strongly. See, for example pages 112-113 in Vrijenhoek and Parker (2009): “The Frozen Niche Variation Model (Vrijenhoek 1978, 1979) was directly stimulated by Roughgarden’s ideas (1972) and a need to explain the stable coexistence of *Poeciliopsis* fish clones in spatially heterogeneous desert streams (Vrijenhoek 1978).”

⁶Soft selection in theoretical population genetics can also mean that the contribution of offspring from different demes in a metapopulation is unrelated to differences in mean fitness among demes.

where selection is both frequency- and density-independent, which is called “hard” selection. For our purposes, we can use Wallace’s terminology to conceptually separate the Tangled Bank Hypothesis from the Lottery Model Figure 2.1.

We can think of the contrast like this. Under the Lottery Model, changes in the environment will select against certain genotypes independent of whether they are common or rare. Selection seems unconditional (hard). Under the Tangled Bank, selection is always conditional (soft); there is an advantage to having a rare genotype, but this advantage only accrues under strong competition (high density). Soft selection may not be exactly the best possible phrase, but it contrasts nicely with hard selection.⁷

Two caveats are worth mentioning with respect to soft selection and the Tangled Bank Hypothesis. One is that polymorphism is only stable under a narrow range of patch-types frequencies. In addition, strong tradeoffs are required for the cost and benefits for morphs occupying different patches (Lively 1986a; Maynard Smith & Hoekstra 1980) (see also Section 3.4). The second caveat is that repeated mutation to asexual reproduction could lead to the accumulation of clonal diversity over time. Once all the niches are occupied by different specialized clones, there would be no advantage to sex. A diverse clonal population could then replace the sexual population (Bell 1982; Vrijenhoek & Parker 2009). This second caveat applies, in general, to any model of sex that relies on frequency-dependent selection. But the ideas could work if mutations to asex are rare. And, as I mentioned, sexuals and asexuals are known to coexist in some populations, which is consistent with the Tangled Bank and Frozen Niche-Variation Hypotheses (Vrijenhoek & Parker 2009). Coexistence, however, is also compatible with the Red Queen hypothesis, which we will now consider.

2.3 The Red Queen Hypothesis

The Red Queen Hypothesis is like the Lottery Model in that it focusses on environmental change over time. However, under the Red Queen idea, the change is mediated by changes in coevolving biological antagonists such as parasites, rather than changes in the abiotic environments.⁸ The distinction is important, as we will see.

It may be helpful to revisit Figure 1.2, which shows the replacement of a sexual population by a clonal lineage within 25 generations. In this example, the clone is a single genotype, while the sexual population is composed of multiple recombining genotypes, only one of which is shared with the clone. Clearly, as the clone spreads, its genotype would become the most common in the host population. Now suppose that the host population is coevolving with a parasite population, which is composed of multiple strains. Assuming random contact between hosts and parasites, the parasite strain that could infect the most common host genotype would have a selective advantage over parasite strains that could only infect rare host genotypes. Let’s call this more successful parasite strain “strain **A**.” What would happen? It should be easy to see that strain **A** would increase in frequency. The parasite population would evolve.

⁷Wallace (1975) explains that the source of the terms “soft” and “hard” stem from financial discussions of soft currencies versus hard currencies in monetary exchanges. Soft currencies only have value within their home country. In contrast, hard currencies can be exchanged overseas for currencies with similar buying power.

⁸I use “parasite” here in the ecological sense to include any organism that lives in, or on, its host, provided it reduces the survivorship and/or fecundity of its host. As such, the term includes both macroparasites (such as worms) and microparasites (such as protozoans, bacteria, and viruses).

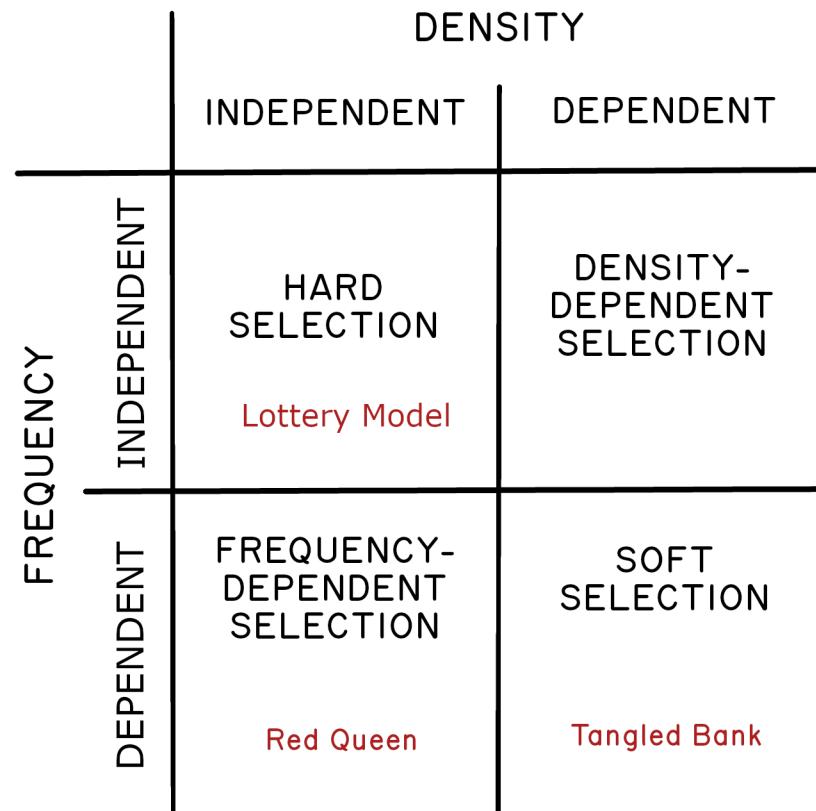


Figure 2.1: Partitioning the ecological hypotheses for the maintenance of obligate sexual reproduction. The figure is redrawn from Wallace (1975). The inserted blue text shows how the ecological hypotheses fit into Wallace's matrix for density-dependent selection versus frequency-dependent selection. The Lottery Model relies on hard selection in temporally variable environments. The Tangled Bank relies on soft selection in spatially variable environments. The Red Queen relies on frequency-dependent selection generated by coevolving antagonistic species.

Now, what if the parasite dramatically reduces the reproductive success of infected hosts? We might expect that, as the parasite evolves to infect the most-common host genotype, the reproductive advantage of the host clone is eroded. Moreover, if the parasite is *common and sufficiently virulent*, evolution by the parasite could prevent the clone from eliminating the sexual population. Under this scenario, there are at least two possible outcomes. One is that the sexuals and asexuals come to exist in stable frequencies, where the lost fecundity of the clone due to infection is equal to the cost of males, meaning that the mean fitnesses of sexuals and asexuals are equal. On the other hand, if the parasite is highly virulent, the frequencies of sexuals and asexuals can oscillate over time (Figure 2.2 A). Under this second scenario, the new clone initially increases, but it is driven down sharply by infection (Figure 2.2 B). Then, once the clone becomes very rare, it should become less infected than observed in the sexual population (Figure 2.2 B). During this period, there is parasite-mediated selection against sex. Hence, the clone increases in frequency (Figure 2.2 A), only to be driven down again by parasites after it becomes common (Figure 2.2 B). Another cycle begins. **The key point is that parasites do not select against clonal reproduction per se; they only select against common genotypes.** But selection against common host genotypes might be sufficient to prevent fixation of a clone in the short term.

This scenario of fluctuating selection for and against sex is just a special case of the more general idea that parasites will select against common genotypes within a diverse, sexual host population. As a rare host genotype becomes common, the parasite genotype that can infect it will be favored by natural selection. If the parasite is virulent (meaning that infection reduces host fitness), the targeted host genotype will decline in frequency, and a new host genotype will begin to increase in frequency. Under this logic, host-parasite coevolution will lead to the oscillation of genotypes in both the host and the parasite populations (Figure 2.3). These oscillations are now called Red Queen dynamics. Red Queen dynamics can lead to the maintenance of genetic polymorphism in sexual populations, and possibly protect sexual reproduction from replacement by asexual lineages. In addition, Red Queen dynamics could also favor recombination within a sexual population (Peters & Lively 1999, 2007; Salathe *et al.* 2008; Schmid-Hempel & Jokela 2002). These related ideas are now called the Red Queen Hypothesis (following Bell 1982).

2.3.1 An intersection of science and literature

The name for the Red Queen Hypothesis comes from *Through the Looking Glass* (Carroll 1872). Here are the relevant bits of the story. After Alice goes through the looking glass (a mirror), she decides to follow a straight path to the top of a hill. But, in following the path, she ends up at her starting point. Talking to herself, she remarks, “But how curiously it twists! It’s more like a corkscrew than a path.” Repeated attempts were unsuccessful. In frustration, Alice addresses a tiger lily amongst a patch of flowers, “I wish you could talk!” The lily informs Alice that all the flowers can talk. The stunned Alice then begins a conversation with the flowers before finally asking, “Are there any more people in the garden besides me?” The rose answers “Yes, there is someone like you.” Alice sets out to follow this person (the Red Queen), but she quickly loses sight of her, and ends up back at her original starting point. Flustered, Alice decides to follow the advice of the rose: “I should advise you to walk the other way.” Alice then quickly finds the Red Queen.

Now it gets especially interesting. Alice mentions to the Red Queen that she would like to “find my way to the top of that hill.” The Red Queen replies, “I could show you hills, in comparison with which you’d call that a valley.” Alice protests: “a hill *ca’n’t* be a valley.... That would be

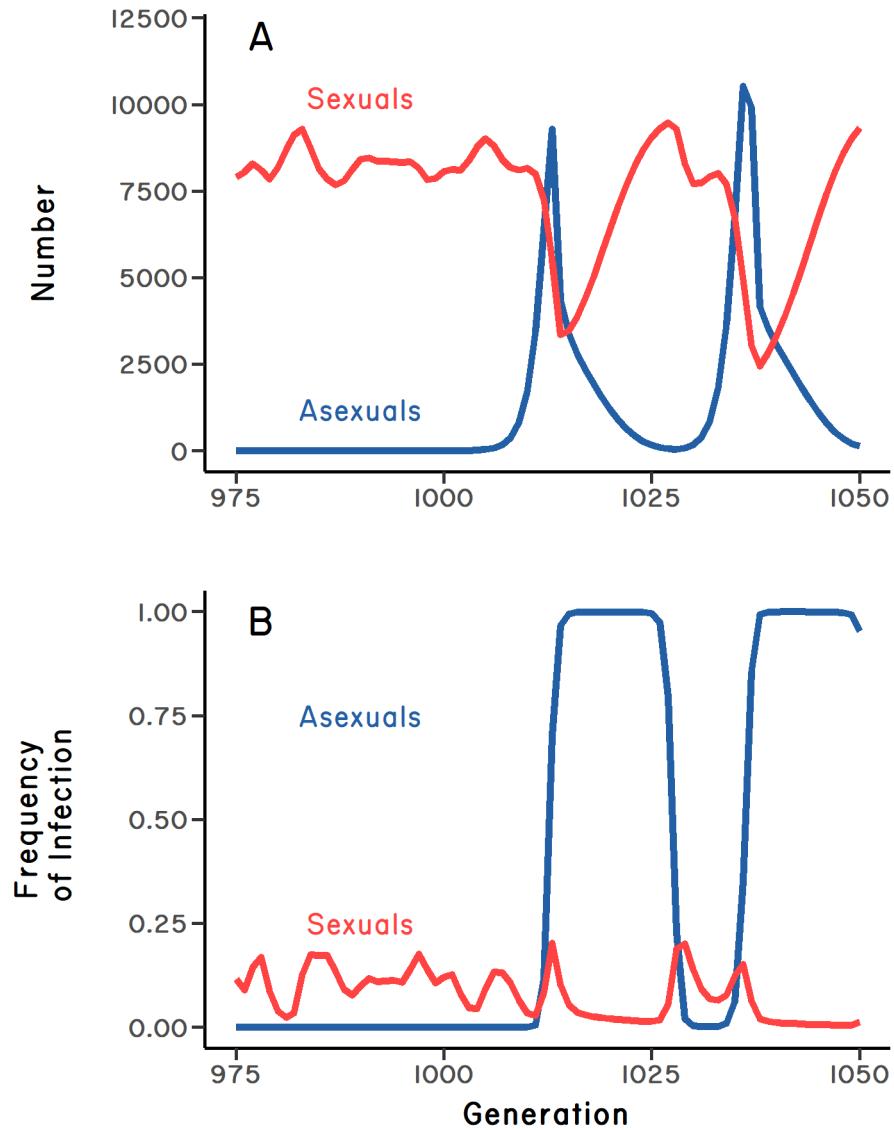


Figure 2.2: Simulation models showing that coevolving parasites can prevent the fixation of asexuals in the short term. **A.** The number of sexual and asexual individuals over time. **B.** The frequency of infection in sexual and asexual individuals over time. The simulation introduces a single clonal genotype into a sexual population at carrying capacity. After the clone becomes common (**A**) the parasites evolve to “target” it for infection (**B**). Note that after the parasites have driven the clone’s frequency down, the asexuals are less infected than the sexuals. Simulation model based on Lively (2009), which treats parasite virulence as a positive function of host density.

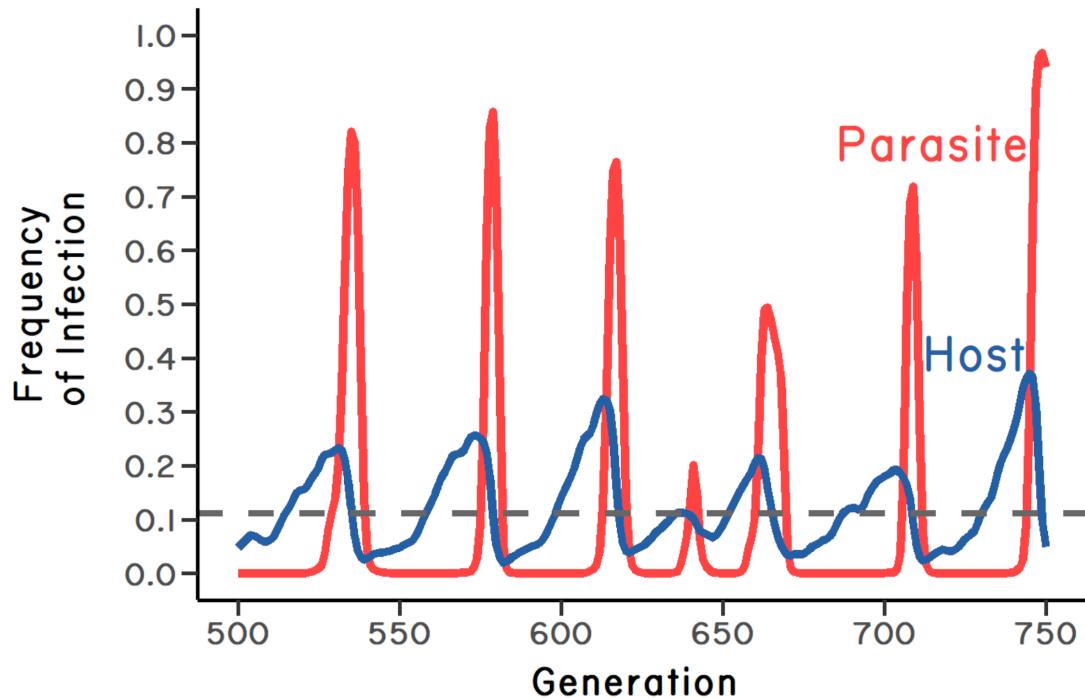


Figure 2.3: Red Queen dynamics. The frequency of a single host genotype is shown along with the frequency of the only parasite genotype that can infect it. Note that the parasite tracks the host with a time lag. Results were extracted from a simulation of a sexual host population with nine possible genotypes coevolving with an asexual parasite with nine matching genotypes (Lively 2009). The dashed line shows the average genotype frequency for hosts and parasites.

nonsense.” This exchange between Alice and the Red Queen now seems prophetic, because, under frequency-dependent selection, locations on the adaptive landscape can rapidly change from fitness peaks to fitness valleys. Perhaps the Red Queen’s statement is correct: hills can become valleys, and valleys can become hills. More specifically, genotypes that were favored by natural selection when rare can become selected against after they become common, leading to a highly dynamic adaptive landscape.

In any case, Alice had clearly entered a crazy world. Straight paths become like corkscrews, progress is made by going the other way, and hills become valleys. Then, suddenly, Alice and the Red Queen began to run: “Alice never could quite make out, in thinking it over afterwards, how it was that they began: all she remembers is, that they were running hand in hand, and the Queen went so fast that it was all she could do to keep up with her.” During this furious run, Alice notices that they never pass anything. The trees remain in the same place as if they were moving along with them. Alice eventually asks: “Are we nearly there?” The Red Queen replies: “Why, we passed it ten minutes ago! Faster!”

When they finally stop, Alice is surprised to be where they started: “I do believe we’ve been under this tree the whole time! Everything’s just as it was!” The Red Queen replies that of course, and then asks: “What would you have it?” Alice replies that she would have expected to get somewhere else after running for a long time. The Red Queen then replies with this very famous quote: “Now, *here*, you see, it takes all the running *you* can do to keep in the same place.” It is a perfect metaphor for host-parasite coevolution.⁹ Host and parasite genotypes might oscillate as if they were running to stay in the same place.

It seems unlikely that Lewis Carroll had coevolution in mind when writing these passages. But he was a mathematician at Oxford University (his given name was Charles Dodgson), and at least one author has shown how his writings can be seen as metaphors for mathematical problems (Bayley 2009, 2010). Along these lines, mathematician Sanderson M. Smith (n.d.) has suggested that [Carroll simply inverted the equation for speed from “speed = distance/time” to “speed = time/distance.”](#) Upon rearrangement, the latter gives “distance = time/speed.” Hence you must run very fast to stay in the same place. But how does the shifting landscape fit in? And why did Alice have to go the other way to meet the Red Queen? I would love to know.

It is perhaps worth pointing out that the phrase “Red Queen Hypothesis” can have two different meanings to evolutionary biologists. In the early 1970s, Leigh van Valen was grappling with data showing that the probability of extinction in very different organisms was independent of the age of the lineage. He reasoned that in coevolutionary interactions, the probability of one species driving the other species extinct could, in fact, be independent of lineage age (1973). It thus seems reasonable to suggest that both antagonists must run (coevolve) as fast as they can to prevent extinction. Graham Bell repurposed the phrase to mean within-population oscillations in host and parasite genotypes (1982). Hence, Van Valen’s idea is about macroevolution (speciation/extinction), while Bell’s idea is about microevolution. Even though van Valen’s use of the Red Queen metaphor was

⁹The intersection between science and literature is not restricted to selection for or against sex. For a fascinating essay on how the biology of parasites meets literature, see Justyna Jajszczok’s dissertation (2017).

published first, I will use Bell's microevolutionary meaning, as it perfectly captures the oscillating nature of genotype frequencies during host-parasite coevolution.¹⁰

2.3.2 Conceptual roots of the Red Queen Hypothesis

Part of my goal is to show science as a process. As such it seems reasonable to discuss the origins of the Red Queen idea. One of the earliest statements alluding to the Red Queen Hypothesis came from W.D. Hamilton (1975). Hamilton was reviewing the books by Williams (1975) and Ghiselin (1974) for the *Quarterly Review of Biology*. Throughout the review, the reader can feel Hamilton's frustration with their arguments. Towards the end, he makes these very abstract suggestions: "[I]t seems to me that we need environmental fluctuations around a trend line of change" and "For the source of these we may look to fluctuations and periodicities ... generated by life itself."

The quote does not specifically refer to parasites, but it does suggest that coevolutionary interactions, in general, could play a role in selecting for sex and recombination. In his memoirs, Hamilton (2001) clears this up, writing, "At that stage when I wrote the review, although I had not seen the particular relevance that parasitism might have, I had for many years seen sex looming ahead and had reached a stage of being excited by the possible primary role of biotic interaction. I had decided that it was in aspects of the interspecies struggle, and not survival in an inanimate environment, that I had to search for the main factor. Adaptation to new physical habitats might be made possible through sexuality but these adaptations could not be the main reason for its existence."

Note that, here, Hamilton is specifically contrasting host-parasite coevolution with the Lottery Model, which relies on random changes in "physical habitats."

At about the same time, a plant population biologist, Don Levin, was also writing on the paradox of sex/rec. In his paper, Levin specifically identified pathogens as a possible force selecting for recombination: "I propose that the persistent tracking of plant hosts by multiple pathogens and herbivores is a prime factor which prohibits the congealing of the genomes of species, especially those in closed communities" (Levin 1975).

Boom! By "prohibit the congealing of genomes," Levin means, "selects for recombination." The reference to "closed communities" means species that are tightly coevolving in the absence of homogenizing gene flow. This quote seems to be the first to specifically identify coevolving pathogens as a primary source of selection favoring the mixing of genomes. Levin's idea was quickly followed by important conceptual contributions by Glesener & Tilman (1978),¹¹ Jaenike (1978),¹² and Lloyd (1980). In particular, Lloyd writes, "[B]iological interactions are more likely than unpredictable physical conditions to provide the kind of relentless, repetitive change that is necessary for sexual parents to be selected because of the genetic diversity that sex engenders." Lloyd then turns this abstract idea into a specific prediction, which I would later test: "If this proves to be so, we will then

¹⁰I. M. Lerner used the Red Queen metaphor as early as 1954 with respect to the selection needed to maintain genetic homeostasis: "The *Alice in Wonderland* situation in which 'it takes all the running you can do to stay in the same place' arises when a stationary level of performance can be maintained only by application of the maximum selection possible" (See page 117 in Lerner 1954).

¹¹For example, Glesener and Tilman write, "Thus, sexuality not only is favored under changed conditions but is itself, capable of changing the conditions. The sexuality of an organism's competitors, predators, parasites, etc., will greatly increase the selective pressure for sexuality on that organism as well" (1978).

¹²Jaenike focuses more on the recycling of genotypes: "My hypothesis differs from Levin's in that sex and recombination are advantageous not to produce novel genotypes as such, but to produce rare genotypes, of which novel ones are only a subset" (1978).

be able to examine whether the occurrence of asexual reproduction is correlated with relaxation of the biological hostility of the environment.” Notice that, in the quotes presented above, both Hamilton and Lloyd were specifically predicting that coevolution is more important in selecting for sex than uncertain physical environments. But it is reasonable to ask, does it really matter? Aren’t both ideas fundamentally about bet hedging in uncertain environments? Yes: I think both ideas are about bet hedging. But the distinction still matters. The Lottery Model is about random shifts in the direction of selection; there is no selection against common genotypes unless the environment changes by chance in a way that disfavors them. By contrast, under the Red Queen, selection is frequency dependent. In fact, selection against common genotypes is the core of the model. Hence, the critical difference between the models is not so much about bet hedging but whether selection for sex/rec is directional (but randomly changing directions, a lottery) or frequency dependent (Red Queen). For example, parasites could be a source of directional selection for sex if they randomly changed which host genotypes they attacked. To my mind, that would be a Lottery Model. The Red Queen Hypothesis requires frequency-dependent selection generated by interactions between species.¹³ This is an important distinction.

Taking this view, the Red Queen Hypothesis may seem more closely related to the Tangled Bank model than to the Lottery Model, as both the Red Queen and the Tangled Bank rely on frequency-dependent selection. But the critical distinction here is that selection against common genotypes under the Tangled Bank relies on intraspecific competition in populations at carrying capacity (soft selection). The Red Queen relies on interspecific antagonistic coevolution, leading to parasite-mediated selection against common host genotypes.¹⁴

In any case, looking back, it seems clear that the architects of the ecological hypotheses had two interrelated things in mind:

1. How can we explain sex/rec?
2. How do we understand the biogeographic and phylogenetic distributions of asexual reproduction?

As an evolutionary ecologist, I was drawn to the confluence of these questions. But other ideas were also interesting, such as the idea that sexual reproduction is favored because it reduces the interference between alleles at different loci (review in Otto 2021). I will cover some special cases of this latter idea in Chapter 6.¹⁵

2.4 Summary

1. Three ecological hypotheses have been proposed to explain the persistence of cross-fertilization in the face of competition with uniparental reproductive strategies, such as parthenogenesis or self-fertilization (following Bell 1982).

¹³I use “frequency-dependent” selection here to mean selection against common genotypes. A more accurate phrase would be “negative frequency-dependent” selection.

¹⁴This is not meant to imply, however, that the strength of parasite-mediated selection under the Red Queen Hypothesis must be independent of population size. Indeed, as we will see, there are good reasons to think that the strength of parasite-mediated selection depends on host density.

¹⁵The basic idea comes from a paper by Hill and Robertson (1966) and is often called the Hill-Robertson effect (following Felsenstein 1974). A broader framework, housed under the more intuitive phrase “selective interference,” was recently given by Sarah Otto as part of a keynote lecture given to the American Genetic Association (2021).

2. The Lottery Model is based on the possible advantages of diversifying offspring facing uncertain changes in the abiotic environment. Here selection is independent of both density and frequency.
3. The Tangled Bank and Frozen Niche-Variation Hypotheses are based on competition for resources when multiple resource types co-occur. Selection is frequency dependent, but the advantage to rare types only occurs when intraspecific competition is intense.
4. The Red Queen Hypothesis relies on parasite-mediated selection against common host genotypes. Such selection, when strong, can result in oscillatory changes in parasite and host alleles. These oscillations are sometimes called Red Queen dynamics.
5. A bet-hedging strategy reduces the variance in reproductive success over time, even if it reduces the arithmetic mean. Sexual reproduction under the Lottery Model is clearly a bet-hedging strategy. The Red Queen idea can perhaps also be seen as bet hedging.

2.5 Appendix: Levene's Model of Multiple Niche Polymorphism

It was widely thought that heterozygote advantage was required to maintain polymorphism at a single locus with two alleles. In the introduction to his paper, Levene wonders “whether it was in fact possible to have an equilibrium without the heterozygote being superior in any single niche” (1953). The paper is not easy to follow, even though the algebra is not difficult. Here I try to simplify the presentation.

Levene first assumes that the proportion of survivors coming from the i^{th} niche is constant (q), independent of the genotypic composition of the niche (i.e., soft selection). He then assumes that the heterozygote has a relative fitness of one in all niches, giving $W_{AB} = 1$. Let q be the frequency of allele A, and let $(1 - q)$ be the frequency of allele B. The frequency of allele A in the next generation, q' , is then

$$q' = \sum c_i \frac{q^2 W_{AAi} + q(1 - q)}{q^2 W_{AAi} + 2q(1 - q) + (1 - q)^2 W_{BBi}}$$

The change in q is simply $q' - q$. Under these assumptions, Levene showed that A allele will increase when rare (barring genetic drift) when |

$$\frac{1}{\sum c_i \frac{1}{W_{AAi}}} < 1$$

where the left-hand side gives the harmonic mean fitness for genotype AA over all niches. The right-hand-side of the equation gives the harmonic mean fitness of the heterozygous genotype, AB, which is equal to one. Similarly, the B allele will increase when rare when

$$\frac{1}{\sum c_i \frac{1}{W_{BBi}}} < 1$$

where the left-hand side gives the harmonic mean fitness for genotype BB over all niches. A genetic polymorphism is expected if both alleles can increase when rare; hence, **polymorphism is expected, in general, when the harmonic mean fitness for the heterozygote is greater than the harmonic mean fitness for either homozygote.**

But does this require that the AB genotype is the most fit in at least one niche? Levene gives a specific example to answer this question. He assumes two niches, where the proportion of survivors from both niches is equal (i.e., $c_1 = c_2 = 0.5$). He then assumes genotypic fitness values, as given in the following table. It is important to note that the heterozygous genotype is not the most fit genotype in either niche.

Table 2.2: Levene's Example

Genotype	Fitness Niche One	Fitness Niche Two	Arithmetic mean	Harmonic mean
AA	$W_{AA1} = 1.50$	$W_{AA2} = 0.67$	1.09	0.93
AB	$W_{AB1} = 1.00$	$W_{AB2} = 1.00$	1.00	1.00
BB	$W_{BB1} = 0.67$	$W_{BB2} = 1.50$	1.09	0.93

For this example, the harmonic mean fitness for the heterozygote is greater than the harmonic mean fitness for either homozygote, thus meeting the conditions given by the equations above. Thus, the answer to Levene's question is Yes. It is possible to have a genetic polymorphism without having heterozygote advantage in any single niche. And, interestingly, the polymorphism is expected even though the arithmetic mean fitness of the heterozygote is less than the arithmetic mean fitness of either homozygote. Finally, based on this example, it seems that a trade-off is required, such that the AA genotype does best in one niche, and the BB genotype does best in the other niche.

Nonetheless, Levene's result suggests that overdominance for harmonic mean fitness is required for multiple niche polymorphism (Prout 1968). However, Timothy Prout showed that a polymorphism could be stable even if one allele is dominant, thus ruling out any kind of overdominance (1968). Let both the AA and AB genotypes have a fitness of one in both niches. Let the BB genotype have a fitness of 0.5 in niche one and a fitness of 1.67 in niche two. Assuming as above that both patches are equally common, we get the following table:

Table 2.3: Prout's Example

Genotype	Fitness Niche One	Fitness Niche Two	Arithmetic mean	Harmonic mean
AA	$W_{AA1} = 1.00$	$W_{AA2} = 1.00$	1.00	1.00
AB	$W_{AB1} = 1.00$	$W_{AB2} = 1.00$	1.00	1.00
BB	$W_{BB1} = 0.50$	$W_{BB2} = 1.67$	1.09	0.77

Prout showed that there would be a stable multiple niche polymorphism even under complete dominance, provided that the arithmetic mean fitness for BB is greater than one and the harmonic

mean fitness for the BB genotype is less than one. So, clearly, overdominance for harmonic mean fitness is not required for a stable polymorphism.¹⁶

The plot below shows Δq as a function of q for Prout's model of dominance. Note that Δq is positive when q is near zero, and that Δq is negative when q is near one. There is an interior equilibrium near $q = 0.5$.

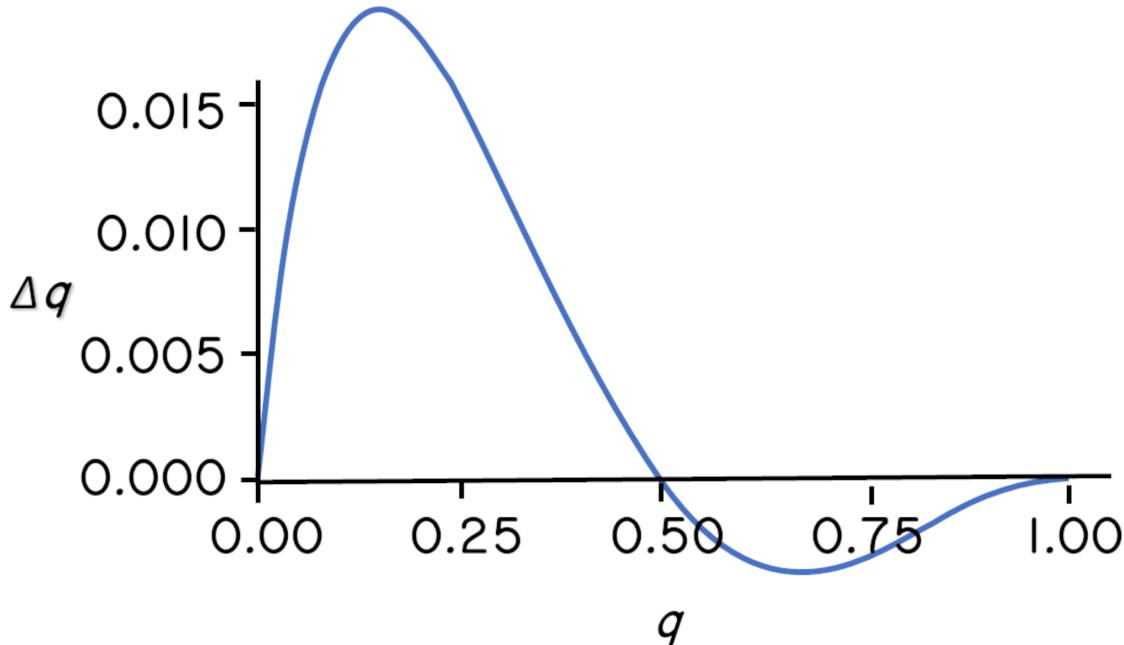
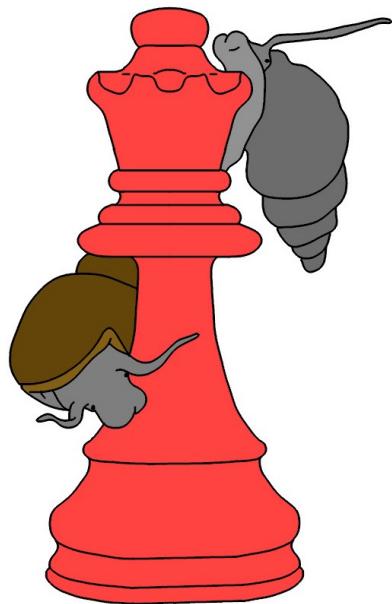


Figure 2.4: Δq as a function of q for Prout's model of dominance

¹⁶The harmonic mean is not intuitive to most Biology students. So, I ask them this question: If you had a score of 100 on your first exam and a score of 60 on your second exam, would you rather have your final grade calculated as the arithmetic mean or the harmonic mean of the two scores? After some thought, they all pick the arithmetic mean. That is because the harmonic mean weights low scores more heavily than high scores.

Chapter 3

Contrasting the Ecological Hypotheses



As I mentioned in Chapter 1, my dissertation focused on intertidal communities. I was especially interested in how two different barnacle morphs coexisted on rocky intertidal shores in the Northern Gulf of California. I had initially assumed that the two types were genetically determined and that

they were likely to be different species (Figure 3.1). However, after years of false starts,¹ I found that one of the two morphs was induced by chemical cues released by a predatory snail (Figure 3.2), and that the induced morph was more resistant to attack by this predator (1986c).² Hence, the two morphs are not different species, but rather the result of phenotypic plasticity. In a blink of a field season, I went from being a community ecologist to an evolutionary biologist.

But why two morphs? Why didn't selection favor unconditional development of the predator-resistant morph? Using predator-exclusion cages, I found that predation was concentrated near crevices in the reef, which the snails used during high tide as refuges (1986b). As the tide receded, the snails moved out from these crevices onto the exposed rock surfaces to forage on barnacles. When the tide returned, the snails motored back to the crevices, presumably to hide from snail-crushing rays that came in with the tide. This back-and-forth movement of snails created high-predation zones near crevices and low-predation zones far from crevices (about 20cm away). This finding explained why the predation-resistant morph was almost always found near crevices. Field experiments also showed that the predator-resistant morph grew more slowly and was less fecund than the typical volcano-shaped morph (Lively 1986b). Hence there is a trade-off. Taken together, the results suggested that plastic development was favored by natural selection to survive in the high-predation zones (Section 3.4). I would later come to think of adaptive plasticity as a type of variation strategy. Sexual reproduction can also be seen as a type of variation strategy (Lloyd 1984). And I was very fortunate to be able to study sexual reproduction after moving to New Zealand.

I moved to New Zealand in 1984 just after defending my dissertation. My reason for moving to New Zealand was simple: my spouse (Lynda Delph) was there. Lynda had moved to New Zealand to study the evolution of plant breeding systems with Professor David Lloyd. I did not have a job, but Lynda had a small stipend from the Fulbright Foundation. By the time I moved to New Zealand, we had only 12 dollars. But Lynda had found a flat in a dormitory at the University of Canterbury, where she worked as a "tutor." Tutors at the time were usually graduate students who served as mentors for the resident students. We made many good friends during our time as tutors, and it was a fascinating total immersion into Kiwi culture. We did not have to pay rent, and we could eat for free in the cafeteria. We could then spend Lynda's small Fulbright stipend on sampling trips.

Then I got very lucky. I was awarded a three-year postdoctoral fellowship from the New Zealand University Grants Committee. I had applied to work on the evolution of facultatively parthenogenetic nematodes, which represented a combination of my interests in developmental plasticity and sex.³ These topics were also very interesting to Wally Clark, a conceptual pioneer in the evolution of plasticity. He was also head of the Zoology Department at the University of Canterbury. I would

¹I ran two years of field experiments designed to test for random settlement by genetically determined morphs. I also ran experiments designed to test for habitat selection by genetically determined morphs. The results were always negative. I finally tested for predator-induced development of the bent morph by placing *Acanthina* snails in quadrats where juvenile barnacles had recently settled. I used herbivorous snails as a control. The results showed that the presence of *Acanthina* induced development of the bent form, but the herbivorous snails did not. It was a thrilling discovery.

²Plasticity is more mainstream now than it was in the 1980s. One reviewer of my paper was incredulous and recommended rejection from *Evolution* because the bent morph was not "genetically determined." The Associate Editor (John Endler) rejected the review and accepted the paper. Clearly, it is the developmental strategy that is genetically determined, not the morph per se (Hazel *et al.* 2004; see also Lively *et al.* 2000).

³Facultative parthenogenesis is used to mean environmentally cued production of parthenogenetic females. I was originally planning to work on a nematode population that produced a mixture of sexual males and females at high density but only parthenogenetic females at low density.



Figure 3.1: The two morphs of the intertidal barnacle, *Chthamalus anisopoma*. **Top**, the “bent” form is induced by exposure to chemical cues released by a specialized barnacle predator, the predatory gastropod *Acanthina angelica*. The bent or “hooded” form reduces the risk of successful attack by this predator. **Bottom**, the typical, conic form of the barnacle. The conic form is more fecund per unit size, and it grows more rapidly than the bent form, but it is also more susceptible to attack by the predator. Drawing by ZMD.

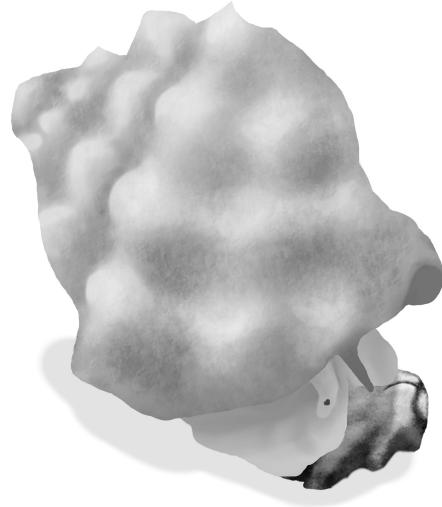


Figure 3.2: Line drawing of the predatory snail *Acanthina angelica* attacking the bent form of the barnacle. Note that the predator has a spine on the outer margin of its shell. The spine is used to push through the opercular plates of barnacles, and it is very effective at penetrating and consuming the volcano-shaped form of the barnacle. The bent form of the barnacle is more resistant to attack of this kind because its aperture is less open to attack from above. Drawing by ZMD.

not have received funding without the support of Professor Clark. To my mind, the value of Clark’s work remains underestimated in general, but it had a big influence on me (e.g., Clark 1976).

I began looking for natural systems to study facultative parthenogenesis.⁴ To this end, I was reading Graham Bell’s incredible book on the evolution and genetics of sexual reproduction (1982). Searching the index, I found a reference to *Potamopyrgus antipodarum*, a New Zealand freshwater snail. Bell had cited Mike Winterbourn’s dissertation work on this snail (1970). Luckily for me, Professor Winterbourn was just down the hall from me. I took the book to him, and I asked if the snails were, in fact, facultatively parthenogenetic. He said no; the snails were probably obligate asexuals, based on lab rearing experiments that he had done. He also said that most populations were all female, but some contained males. He then added that there was no obvious pattern to the distribution of males. Amazing! I immediately decided to work on these snails.⁵

3.1 The Method of Multiple Working Hypotheses

As graduate students at the University of Arizona, we read some of the classics in the history and philosophy of science. Two of these papers concerned the method of contrasting multiple

⁴We were trained ask questions first and then seek suitable organisms to address the questions. This was the tradition before model-systems research took over (Churchill 1997).

⁵Professor Winterbourn was supportive of my work from this first day. He shared his knowledge of the snail system and of freshwater ecology, in general, with great enthusiasm. In addition, Mike met with my Ph.D. students and took them into the field. This book would not have been possible without Professor Winterbourn.

working hypotheses (Chamberlin 1890; Platt 1964).⁶ The idea is that multiple hypotheses should be simultaneously considered. Then, to the extent possible, the alternatives are forced to make different *a priori* predictions about the possible results. The hope is that all but one of the alternative hypotheses would be eliminated, leading to a “strong inference” that the remaining hypothesis is supported (Platt 1964). Thus, the focus is on falsifying one or more of the alternatives, rather than proving one of them (Popper 1959). Graham Bell used this same method to contrast the ecological models for sex by using data on the geographic distribution of asexual individuals across many plant and animal taxa (Bell 1982). The data led him to reject the Lottery Model (Chapter 2). I decided to focus a similar test directly on the New Zealand snails (Figure 3.3).



Figure 3.3: The freshwater snail *Potamopyrgus antipodarum*. This small (3 – 6 mm) prosobranch snail evolved from marine ancestors (Phillips & Lambert 1990). Associated with the invasion of freshwater, the snail evolved an internal brood pouch, where the embryos hatch and develop before crawling out as juveniles. The snail also evolved parthenogenetic reproduction. Parthenogenesis and brooding are both rare traits in invertebrates, but they are often found together (Lively & Johnson 1994). Some *P. antipodarum* populations presently consist of a mixture of diploid sexual individuals and polyploid asexual females. The question under consideration here is, why have the sexual females persisted in these mixed population snails? What are the advantages of sexual reproduction? Photo credit: © Bart Zijlstra.

⁶See also Elliott and Brook (2007). They point out crucial differences between Chamberlin and Platt including that Chamberlin allowed for multiple ideas to be partially correct, which is important for Chapter 6.

The snails (*Potamopyrgus antipodarum*) are often called mud snails, but I think the term is a misnomer. They live on rocks and vegetation in some of the most beautiful clear lakes, rivers, and streams in New Zealand (“Potamo” means river, not mud, in Greek). In any case, based on Winterbourn’s ecological work, streams seemed more unstable than lakes, as water flow can vary dramatically, especially during heavy rains in the mountains (Winterbourn *et al.* 1981). Hence, under the Lottery Model, streams should have more sexual females (and males) than lakes, because streams have more disturbance and less competition (see Chapter 2 for a comparison of models). By contrast, it seemed that competition for resources should be greater in lakes than in streams. Indeed, lake populations of the snail can be extremely dense. So, under the Tangled Bank, there should be more sexual females in lakes, where competition for resources is expected to be high. Finally, under the Red Queen Hypothesis, there should be more sexual females where the risk of infection by coevolving parasites is higher. As such, the different hypotheses could be forced to make different predictions, with the important caveat that infection might be correlated with habitat.

Some clarification regarding the prediction of the Red Queen Hypothesis might be useful here. Some people have asked me why the correlation between sex and infection is expected to be positive if, indeed, parasites are the selective force for sexual reproduction. For example, one could ask, if sex is so helpful in reducing infection risk, then shouldn’t the highly sexual populations have fewer, not more, parasites? That could, of course, be expected in an experiment where hosts across all populations were exposed to the same number of parasites. Then the more genetically diverse populations with higher frequencies of sexual females might be expected to have a lower prevalence of infection. But it is not the case that all natural populations have the same risk of infection. The idea under the Red Queen Hypothesis is that asexual females would replace sexual females where the risk of infection is low, and that sexual females would persist where the risk of infection is high, provided that the parasites are highly virulent. That is how the positive correlation could be generated. Nonetheless, the data could be expected to be very messy, especially if the frequency of sex oscillates over time in response to coevolutionary games with parasites.

The snails are infected by trematode worms, but I did not know anything about trematodes when I first began dissecting snails. I was just looking for males. Winterbourn told me that I would know a male snail when I saw one, as they have a penis just behind the right tentacle. But I had not observed any such structure on the many snails I collected from the streams around the university. I was beginning to think that I was missing something. Then one day, when I was dissecting a snail, hundreds of swimming things came out. Sperm, I thought. My first male! I took them to Wally Clark’s research technician, Jan McKenzie, to put under her fancy microscope. She informed me that sperm do not have eyes, that they do not have spines on their tails, and that they are, in fact, orders of magnitude smaller than these wiggling beasts under her lens. She was not impressed. I had perfectly fit the Kiwi stereotype of North American ecologists: good with statistics but no knowledge of real animals. She informed me that these swimming things were trematode larvae, **sterilizing parasites** of snails. Happily, we remained good friends, despite her disappointment in my training. And I had found my first infection, which meant that I might be able to test the Red Queen.

Perhaps embarrassingly, I had a scientific bias against the Red Queen going into the study. My bias was based on a study by May and Anderson (May & Anderson 1983). They showed that parasites had to kill infected individuals for sex to be favored over asex in hosts. Parasites are usually not that virulent; hence, it seemed to me that parasites could not provide sufficiently strong selection

to *generally* favor sex. I will return to this important paper in another chapter and discuss how key assumptions of their model have been relaxed.

3.1.1 A side story on JMS

John Maynard Smith (JMS) was one of the most influential theoretical biologists in history of evolutionary thought. He was able to formulate and communicate novel ideas with apparent ease. Around the time that I was beginning to work on *Potamopyrgus*, JMS came to New Zealand, along with his wife, Sheila. He was invited by David Lloyd to spend time at University of Canterbury and to deliver three public lectures, which were all fantastic. During this time, JMS spent several weeks in New Zealand. Lynda, David, and I were lucky enough to hang out with him quite a bit. JMS was a remarkable individual. He could talk with anyone and show a sincere interest in their work. One morning, I was sitting next to JMS in the tearoom in the old Zoology Department. I was scared speechless. He kindly asked me what I was working on, so I told him about the snails. He knew of them! In fact, he had covered them in his book, *The Evolution of Sex*.⁷ He was very excited that I was working on these creatures, and he wanted to know my plan. I told him of my rough ideas for looking at the distribution of males as a way of contrasting the ecological hypotheses for sex. He looked directly at me, and said, “Interesting, but I hope the answer is not parasites” (or something like that). I asked him, why not parasites? He laughed out loud, and with a big smile he said: “Because Bill Hamilton thought of it first!” I could tell he was kidding. He then encouraged me to take the project on, and then he laughed again and added, “Whatever you do, don’t go and solve the problem of sex. Sex is too much bloody fun to have an answer!”

Toward the end of their time in New Zealand, JMS, Sheila, David, Lynda, and I did a trip together around the South Island. The whole time was incredible. Just listening to David and John talk about evolutionary theory was a scientific dream. Towards the end of our trip, we were all together in a restaurant at the Hermitage (near Mt. Cook) on the night that JMS turned 65 and formally retired. Our server, a young alpinist working to support his climbing in the Southern Alps, asked JMS, “I think that I saw a documentary about you. Are you famous?” JMS (smiling and intrigued) asked the alpinist what he remembered. Without hesitation, the alpinist recited a perfect overview of evolution by natural selection. JMS was clearly touched. Almost exactly half-way around the world from Sussex England, in a small township in New Zealand, JMS met someone whom he had influenced with his work. And this was on the very night of his retirement.

The next day, we drove to a small lake near Mt. Cook that David knew about: Lake Alexandrina. It was a glorious day, and we decided that we might as well collect some snails. JMS waded into the water and proceeded to collect a handful of *Potamopyrgus* from the shallow rocks. He handed the snails to me. He then laughed and said, “When you publish your study, I want to know the outcome for these exact snails.” As it turned out, Lake Alexandrina has a mixed population of sexual and asexual snails, and it has been the primary focus of our long-term studies on *Potamopyrgus*. The snail team still refers to this original site of collection as “JMS.” Interestingly, JMS is one of the most dynamic sites in the whole lake.

⁷With respect to *Potamopyrgus* (along with a parthenogenetic beetle) Maynard Smith (1978) wrote, “Further Investigations of these cases could be most interesting.” When I met JMS, I did not know (or did not remember) that he had written this. But I think that he was correct.

3.2 The Distribution of Male Snails

To contrast the alternative ecological hypotheses, I sampled snails from lakes and streams across the South Island of New Zealand. I could drive Lynda's Volkswagen bug to most of the lakes, but I had to backpack into many. Unfortunately, my time working in the Sonoran Desert had not prepared me for the steep climbs, heavy rains, and chest-deep river crossings on the South Island. I did not take enough food or dry clothes on one trip, and my desert hiking boots disintegrated. I got my butt kicked. But it was wonderful to have an excuse to see remote parts of the South Island, especially after I got better gear and gained a better understanding of the New Zealand bush.

I collected and dissected hundreds of snails from each of 29 streams and 22 lakes, mostly on the South Island. I recorded sex (male or female) and infection by the trematodes that Winterbourn (1973) described. I reasoned that the frequency of males in a population must be strongly correlated with the frequency of sexual females simply because males are only produced by sexual females.⁸ The results showed that there were more males in lakes than in streams, which was inconsistent with the Lottery Model, but it was consistent with the Tangled Bank Model. However, male frequency was better predicted by the frequency of trematode infection than by habitat *per se* (Lively 1987). Hence, surprisingly, the results favored the Red Queen Hypothesis. I presented these findings to a small group at David Lloyd's flat, and they convinced me to submit to *Nature* (1987).⁹

A fascinating paper on the same topic was published in *Nature* at about the same time. This paper was also based on a strong-inference test comparing the Red Queen and the Tangled Bank. The authors, Austin Burt and Graham Bell, examined recombination in mammals (1987). They reasoned that under the Red Queen Hypothesis, longer-lived mammals would have higher rates of recombination because more genetic mixing would be favored as the asymmetry in host/parasite generation time increased. In contrast, the Tangled Bank Model predicted that shorter-lived mammals would have higher rates of recombination because they have larger litters, and recombination might lead to reduced competition among the more diverse offspring. Their results were stunning. Recombination was tightly and positively related to longevity in natural populations.¹⁰ The Red Queen was again supported.

Based on these studies in *Nature*, I was beginning to think that parasites might be a factor in selecting for cross-fertilization in hosts. But my study as well as the study of Burt and Bell (1987) were based on correlations. And every scientist knows that correlation is not causation. On the other hand, these correlations were predicted *a priori* by Lloyd (1980) and others (Bell 1982; e.g., Glesener & Tilman 1978). The Red Queen was supported by the data, but the data were not used to generate the hypothesis. Using the same data to both generate and substantiate hypotheses is where the problem arises with correlation, especially when multiple factors are considered in “fishing expeditions.” But forcing different hypotheses to make different *a priori* predictions about the direction of correlations is, to my mind, a powerful way to evaluate alternatives.

⁸This assumption turned out to be not strictly true. Polyploid females occasionally produce males, although they seem unlikely to be very fertile (Soper *et al.* 2013).

⁹The group included Mark McKone. Mark was a post-doc with David, and his comments were especially influential. Fifteen years later, I would become Ph.D. advisor to one of Mark's star mentees at Carleton College, Maurine Neiman.

¹⁰There were also some very interesting outliers. Domesticated mammals had very strong positive residuals for the rate of recombination. This result suggests that recombination was selected by frequent changes in the targets of artificial selection by humans.

As a brief aside, I cannot help but mention the human toll taken by R.A. Fisher's use of "correlation is not causation" as a way to plant doubt in the mind of smokers about the now-obvious risks of smoking (Gould 1991; Stolley 1991). Fisher was a consultant for the tobacco industry, and he did the industry a great service at the cost of human lives. I would also add that no test statistic is causation; F statistics derived from analysis of variance are not causation. Causation might be inferred from well-designed experiments, but no statistical test is causation. Analytical theory is not causation either, as is well demonstrated by the theoretical literature on sex/recombination. Causation instead may be inferred when multiple independent lines of evidence point to similar solutions. I think that Levins (1966) was correct when he wrote, "Hence our truth is the intersection of independent lies."¹¹ Although he was referring specifically to mathematical models, the same principle applies to biological systems. Ideally, the multiple lines of evidence would include long-term field observations of individual populations, broader biogeographic patterns across populations, and direct experiments on multiple independent systems, as well as multiple theoretical forays into the conditions under which the hypothesis is expected to hold.

In any case, my view by 1987 was that the Red Queen Hypothesis merited serious consideration.¹² For my own data, I now asked whether the correlation between sex and infection was a "red herring." In other words, could the correlation be generated because of something else? Yes, it could. Here is how it might work. First, infection could be higher in dense host populations as expected under theory (Anderson & May 1979; May & Anderson 1979). Second, there might be more sex in dense populations because asexual reproduction is favored in sparse populations as a way for individuals to ensure reproduction even in the absence of conspecific mates (Gerritsen 1980; Lloyd 1980; Tomlinson 1966). This latter idea is called the "Reproductive Assurance Hypothesis." Hence, one could find a positive correlation between sex and infection as a simple consequence of epidemiology and selection for reproductive assurance. So, I decided to sample again, this time focusing on South Island lakes (Figure 3.4 & Figure 3.5) while also collecting data on snail density. The results were consistent with the epidemiological expectations, as there was a marginally significant positive relationship between snail density and infection prevalence, but there was no support for the Reproductive Assurance Hypothesis (Lively 1992). Finally, the previously observed positive relationship between sex and infection held (Figure 3.4).¹³ The Red Queen was still in the running.

These results suggested that parasite-mediated selection might contribute to the persistence of sex in mixed populations of sexual and asexual snails. It is of particular interest, perhaps, to note that there are no populations with a high proportion of males in samples where parasites were rare or absent (Figure 3.4). This finding is consistent with David Lloyd's 1980 prediction that asexuals

¹¹From Levins (1966): "Therefore, we attempt to treat the same problem with several alternative models each with different simplifications but with a common biological assumption. Then, if these models, despite their different assumptions, lead to similar results we have what we can call a robust theorem which is relatively free of the details of the model. Hence our truth is the intersection of independent lies."

¹²I was also persuaded by elegant experimental studies on sweet vernal grass, which showed a density-independent advantage to having a rare genotype (Antonovics & Ellstrand 1984; Ellstrand & Antonovics 1985). Later studies showed that the rare advantage was likely due to escape from infection (Kelley *et al.* 1988; 1993, 1994).

¹³The partial correlation between percent male and prevalence of infection, while controlling for habitat, is highly significant ($r = 0.36$, $P < 0.001$). However, the partial correlation between percent male and habitat, while controlling for prevalence of infection, is marginally significant ($r = 0.21$, $P = 0.05$). Similar results were gained after males were excluded from the calculation of infection prevalence, which controls for any sex-specific differences in susceptibility (as shown in Figure 3.4); specifically, prevalence of infection in females was significantly correlated with male frequency while controlling for habitat ($r = 0.37$, $P < 0.001$), but the converse was not true ($r = 0.19$, $P = 0.06$).

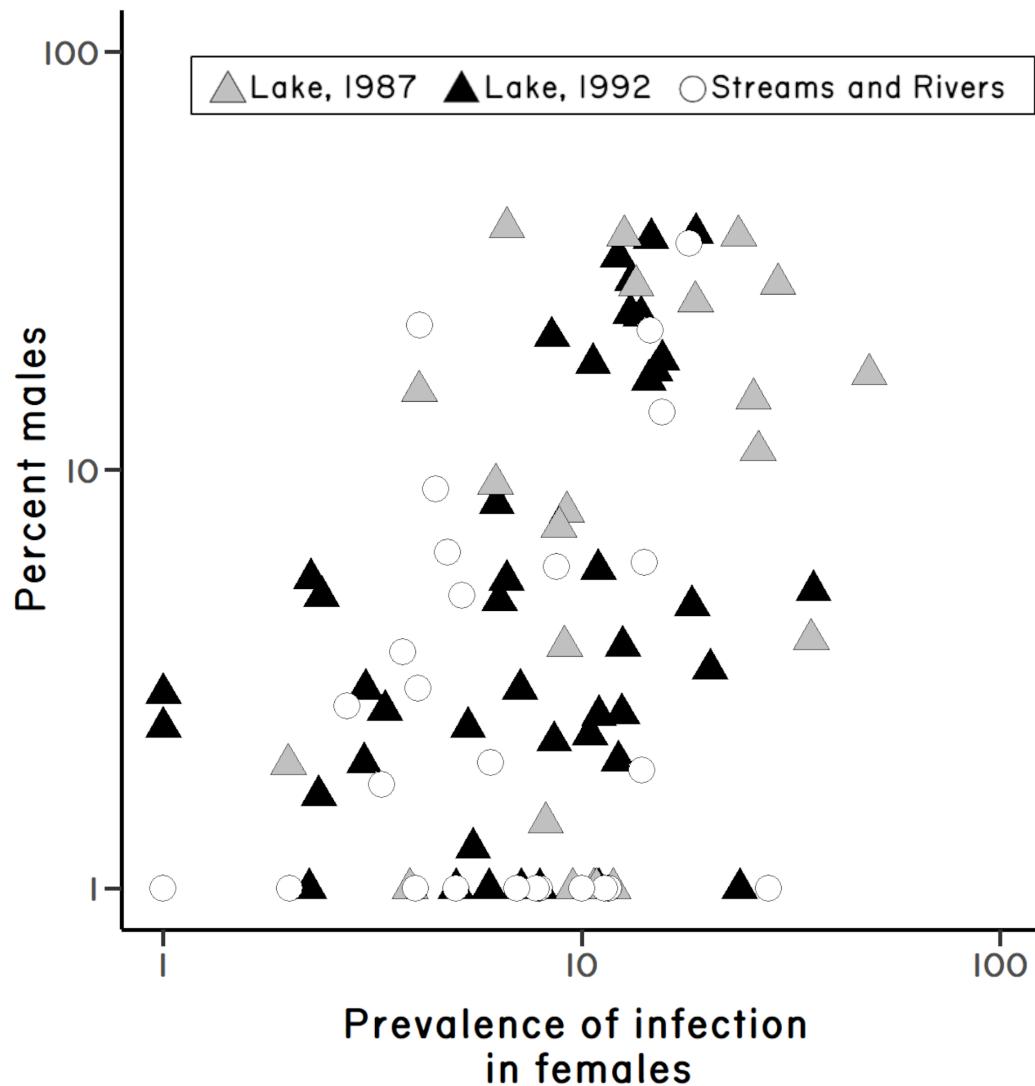


Figure 3.4: Results from surveys of New Zealand lakes and streams showing percent males against the prevalence of female infection by all species of trematodes. Note the upper left side of the graph. There are no highly sexual populations where parasites are rare or absent, which suggests that asexuals have replaced sexuals where parasite-mediated selection is weak. This result is consistent with Lloyd's prediction given in Chapter 2. Circles represent stream populations (Lively 1987) plus two river samples. Gray triangles represent lake populations (Lively 1987). Black triangles represent lake and tarn populations (Lively 1992). The correlation is positive and statistically significant.

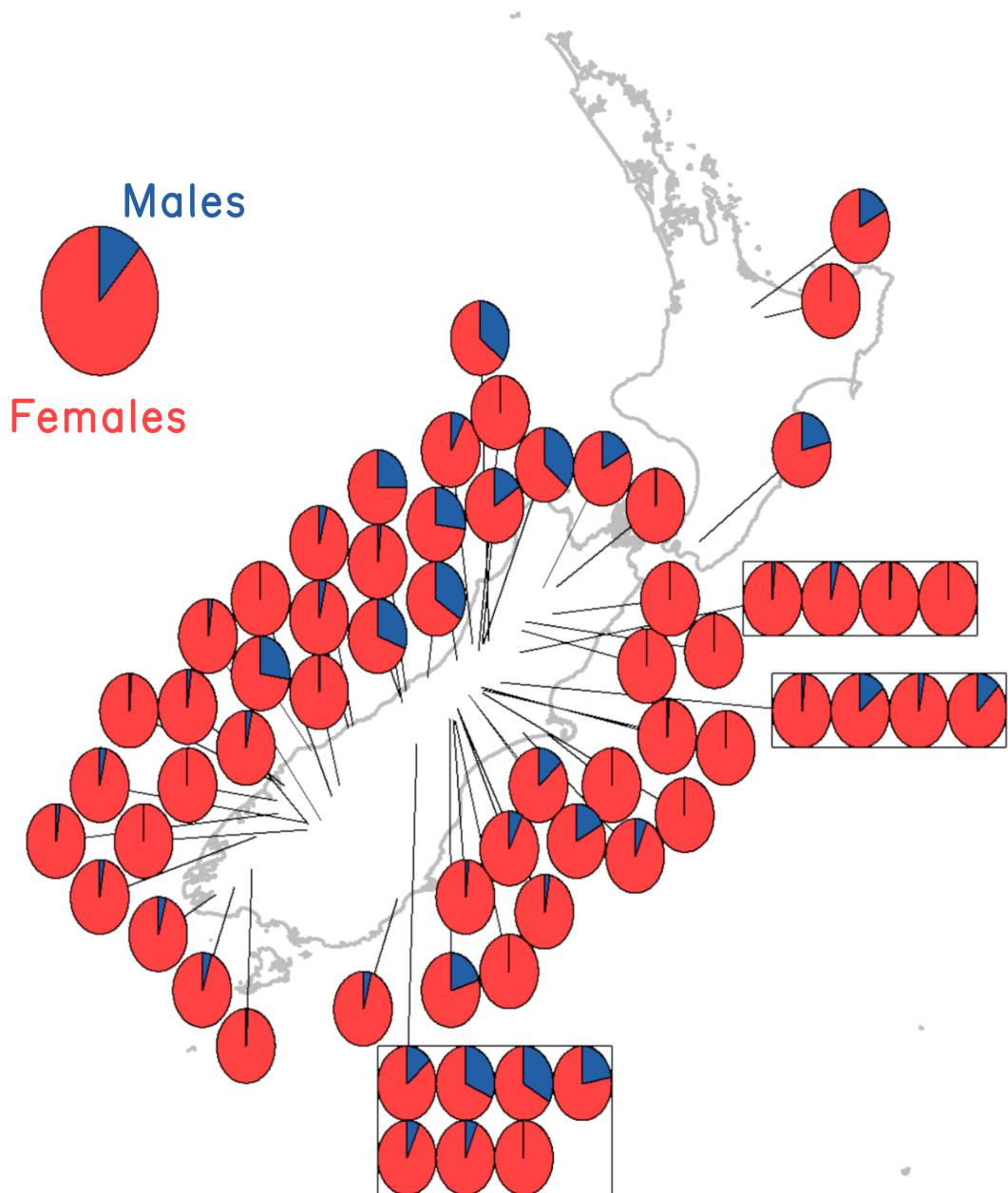


Figure 3.5: The distribution of male and female *Potamopyrgus antipodarum* across New Zealand. The percentage of males is given in blue; the percentage of females is given in red. Pie charts enclosed in boxes are for lakes and tarns that are very close together. The large pie on the left-hand side shows the average frequencies of males and females across all samples. (Redrawn from Lively 1992.)

should dominate in populations “with a relaxation of biological hostility” (see above) (1980). But the results are messy.

There are several reasons for why the results might be expected to be messy. One is that prevalence of infection might not give a good estimate of the strength of parasite-mediated selection (Lively 2001). For example, infected snails might die at a faster rate than uninfected snails because of the energetic demands of infection. In addition, infected snails are more likely than uninfected snails to forage after sunrise, which exposes them to predation by their final hosts, ducks (Levri & Fisher 2000; Levri & Lively 1996). Prevalence of infection might also fluctuate over time as the genetic diversity in the host population changes and/or as the final hosts move among locations. We now know that the prevalence of infection varies greatly among years and among sites in the same lake (Gibson *et al.* 2016). Thus, detecting a significant correlation between sex and infection could be dicey, even if parasites were solely responsible for the short-term maintenance of sex in mixed populations.¹⁴

Along these lines, many of the points in Figure 3.4 represent a single sample taken at one site at one point in time. This limitation likely introduces “noise” into the data, especially for samples where parasites are only periodically common. For this reason, Jukka Jokela and I selected 20 of the best sampled lakes from the data set given in Figure 3.4.¹⁵ We resampled all 20 lakes 10 – 15 years after my original samples. We found that prevalence of infection was highly correlated between sample periods as was male frequency (Lively & Jokela 2002). We then averaged the data for each lake under the assumption that the averages would better represent both the frequency of males and the prevalence of infection for each lake. With these data, the correlation between male frequency and infection prevalence was both positive and significant.¹⁶

None of this is meant to imply proof of the Red Queen Hypothesis or that density dependence and random environmental change are not relevant for a full understanding of the problem.¹⁷ But the results do imply that the Red Queen Hypothesis was (and still is) worthy of further study.

3.3 Summary

1. The co-occurrence of discrete morphs is inherently interesting to evolutionary biologists. Genetic diversity is also inherently interesting.
2. Some populations of the New Zealand freshwater snail, *Potamopyrgus antipodarum*, contain both sexual and asexual females. Other populations are mostly or completely parthenogenetic. This makes the snail a very useful natural system for contrasting alternative hypotheses for the maintenance of sexual reproduction.

¹⁴Using computer simulations, we recently found that detecting a significant positive correlation between clonal diversity and infection prevalence would only be expected in a fraction of parameter space, even when parasites were solely responsible for the maintenance of diversity (Lively *et al.* 2021).

¹⁵In this smaller sample of 20 lakes, the correlation between male frequency and infection prevalence was positive but not statistically significant.

¹⁶ $r = 0.47$; $P = 0.04$ for \log_{10} transformed data; $N = 20$.

¹⁷I think density dependence is critically important. Disease transmission is certainly density dependent (Anderson & May 1979; May & Anderson 1979). Virulence may also be density dependent (Bell *et al.* 2006; Lively *et al.* 1995; Lively 2006). Habitat partitioning may also play a role in the distribution of sexual females among depth-stratified habitats (Negovetic & Jokela 2001).

3. The prevalence of sterilizing trematode larvae is a better predictor sexual reproduction in the snail than habitat (lakes versus streams), thus favoring the Red Queen Hypothesis over the alternative ecological hypotheses.
4. Comparing the *a priori* predictions of multiple working hypotheses can be helpful to evaluate competing ideas. Field studies of natural systems may be required to fully understand why cross-fertilization is so common.

3.4 Appendix: Game-Theoretic Model

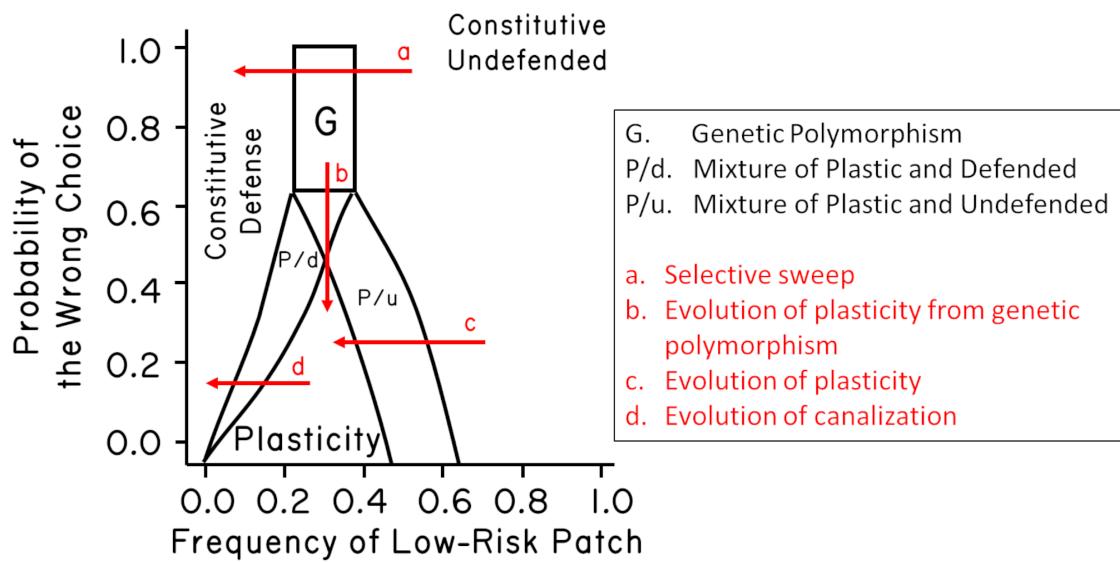
As part of my dissertation research, I constructed a game-theoretic model of selection on three strategies:

1. canalized development into a high-fecundity morph,
2. canalized development to a low-fecundity, predation-resistant morph,
3. induced development into the low fecundity defended morph in the presence of predators.

The model examined evolutionary stability for a range of frequencies for two patches (high predation risk and low predation risk) across a range of values for the accuracy of the cue predicting future predation risk (Lively 1986a).

An example of the output is shown below. The results show that any of the three strategies can be an ESS in part of the parameter space.¹⁸ High reliability of the cue and intermediate patch frequencies favor the plastic strategy. Genetic polymorphism is expected under a relatively narrow set of conditions. Mixtures of constitutive and plastic strategies can also be stable. Note that changing the patch frequencies leads to evolutionary change. For example, reducing the frequency of the low-risk patch can lead to a selective sweep (arrow a). It can also lead to the evolution of plasticity (arrow b) and the evolution of canalized development (arrow c). Increasing the accuracy of the cue can also lead to the evolution of plasticity. It might be especially interesting to note that the trajectory of arrow b would give the appearance of saltatory change followed by stasis (i.e., punctuated equilibrium) (Levinton 1988). Also note that the conditions for a genetic polymorphism are relatively narrow. Redrawn from Lively (1999a) assuming a small cost to plasticity.

¹⁸“Parameter space” represents all possible combinations of variables as defined by the model. In Section 3.4, different strategies are favored for different combinations of variables (i.e., different parts of the parameter space).



Chapter 4

Self- / Non-Self-Recognition and Local Adaptation



One way to falsify the Red Queen is to experimentally show that the expectations of the hypothesis are not met. One expectation is that parasites would quickly become adapted to infecting their local host populations. Here is the logic. If parasites are closely tracking common host genotypes in their local (sympatric) populations, then they should be better, on average, at infecting sympatric hosts than foreign (allopatric) hosts. If this is not the case, then parasites would seem unlikely (at least to me) to be a factor selecting for sexual reproduction.

I am often asked why we would expect the parasites to be better at infecting their local hosts instead of the opposite. Why shouldn't hosts evolve to be more resistant to their local parasites than to allopatric parasites? It is a fair question. One common answer is that parasites are locally adapted

to host populations because they have faster generation times. But that cannot be the whole answer. Theory has shown that parasites can be locally adapted even when there is no generation-time asymmetry (Gandon & Michalakis 2002; Lively 1999b). Instead, I think the answer has more to do with the underlying genetic basis for infection.

What, then, is the genetic basis for infection? This was unknown, but I was assuming that all animal hosts have a self- / non-self-recognition system, such that they can detect foreign tissues (e.g., parasites or tissue grafts) that do not match their own. Sponges, for example, accept tissue grafts from self, but reject grafts from unrelated individuals of the same species (review in Elda Gaino & Magnino 1999). This ability to reject foreign tissues seems widely conserved (Buss 1990). I was also assuming that the self- / non-self-recognition system is genetically variable and that different host genotypes would dominate in different populations. Parasite genotypes that match the most common local host genotypes would be favored by natural selection, and these parasite genotypes should increase in frequency. This should lead to local adaptation by the parasites. Fortunately, one can test for local adaptation using reciprocal cross-inoculation experiments.

4.1 Experimental Studies of Local Adaption

While I was still a post-doc in New Zealand, I set up two reciprocal cross-inoculation experiments to test for local adaptation by the parasites. I knew from my field surveys that one species of sterilizing trematode was especially common in lake populations of the snail. This species was not formally described, but Jan McKenzie sent it to a trematode expert in France, who thought it belonged in the genus *Microphallus*; hence I will refer to it as *Microphallus* sp.¹ The life cycle of *Microphallus* turns out to be especially crucial to the story. The adult worms are tiny simultaneous hermaphrodites that live in the intestines of ducks. They cross-fertilize and produce eggs that are shed with the duck feces into the environment. In most trematodes, the eggs normally hatch in water, thereby releasing a swimming larval stage (miracidia), which actively swims to and penetrates the body of snails. This is the case for the trematodes that cause the human disease, Schistosomiasis. But, in this New Zealand species of *Microphallus*, the eggs hatch not in the environment but rather after being ingested by snails. The larvae then penetrate the snail from the inside. If the snail's immune system does not recognize the larvae as foreign tissue, the larvae reproduce asexually, producing several hundred cysts (metacercaria) in the snail. These cysts completely replace the reproductive tissue in both males and females. Infected snails are sterilized (Figure 4.1; Figure 4.2).

I set up an experiment in which I exposed snails from two different lakes to *Microphallus* eggs from both lakes. One lake was on the east side of the Southern Alps (Lake Alexandrina), and the other lake was on the west side of the alps (Lake Mapourika). I reasoned that gene flow between the two lakes was likely to be very low, so it seemed unlikely that gene flow could swamp out parasite-mediated selection (if present). But to get the eggs, I had to first complete the life cycle of the parasite in the lab. This had never been done. Eventually, I took the advice of Dr. David Blair, a friend and parasitologist at the University of Canterbury: I fed the cysts to lab mice. I then collected the mouse poo, washed it, and fed the slurry to snails. It seemed very unlikely to work, as ducks (not mice) were the vertebrate host, but I tried it anyway. It worked! I was able to experimentally

¹The trematode worm was not formally described until 30 years later (Blasco-Costa *et al.* 2019). As it turns out, it belongs in the genus *Atriohallophorus*, rather than *Microphallus*, and it was very appropriately named after Mike Winterbourn: *A. winterbourni*. But I am going to call it *Microphallus* in this book, as that is what we called it in our early papers.

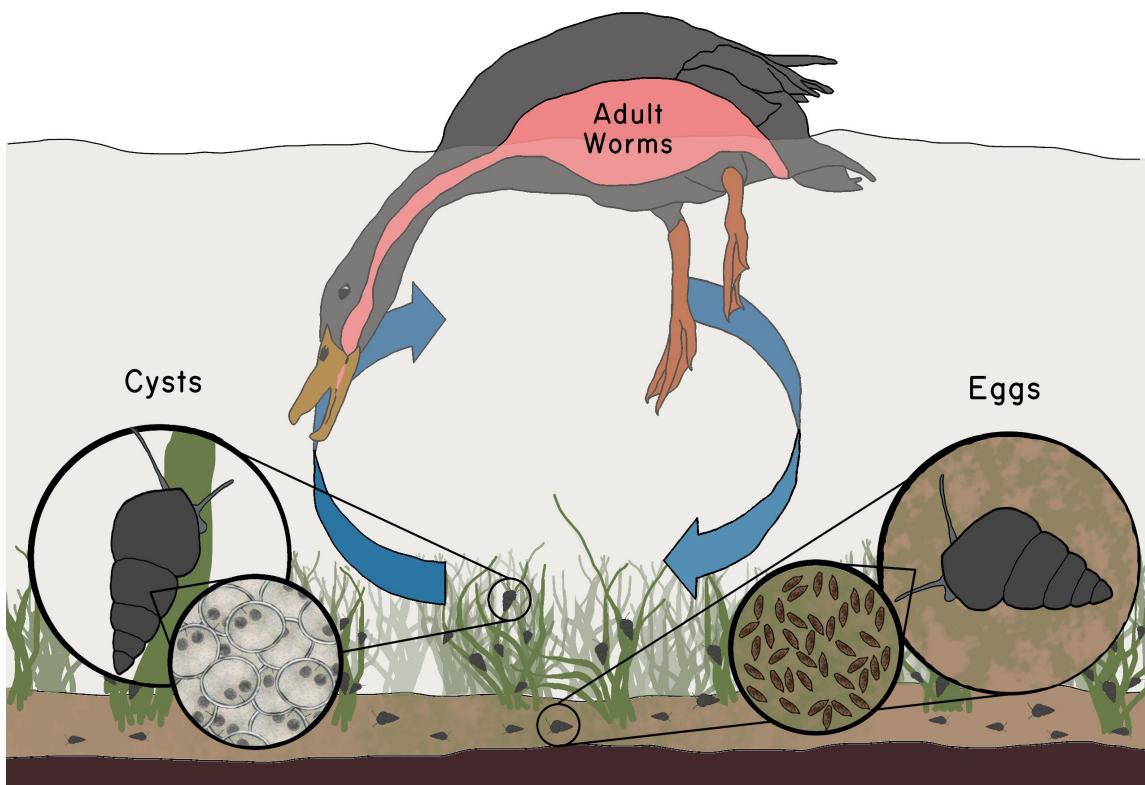


Figure 4.1: The life cycle of the trematode *Microphallus*. The adult worms live in the intestines of waterfowl and wading birds (black stilts). They produce cross-fertilized eggs, which are released into lakes and streams with the bird's feces. The eggs hatch following ingestion by snails. Infection results in the asexual production of hundreds of cysts (called metacercaria). These cysts "hatch" and mature following ingestion by ducks, thus completing the life cycle. Drawing by Zoe M Dinges.

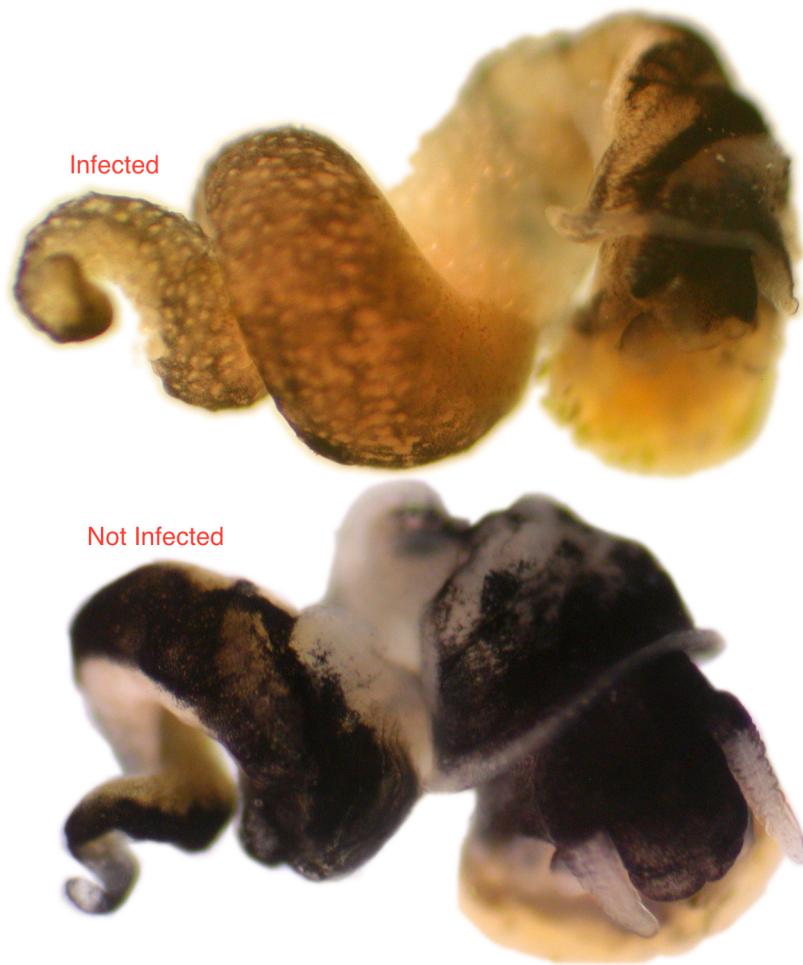


Figure 4.2: Infected female (top) and uninfected female (bottom) of *P. antipodarum*. The snails had been removed from their shells. The golden cysts in the infected female (top) are *Microphallus* metacercaria. The white tissue of the uninfected female (bottom) is ovary. (Photo Credit: Gabe Harp)

infect snails in the lab. And, amazingly, the parasites from both lake populations were much more infective to snails from their same lake (Figure 4.3). In other words, the *Micophallus* parasites were locally adapted (Lively 1989). There was no reason based on this experiment to discard the Red Queen.

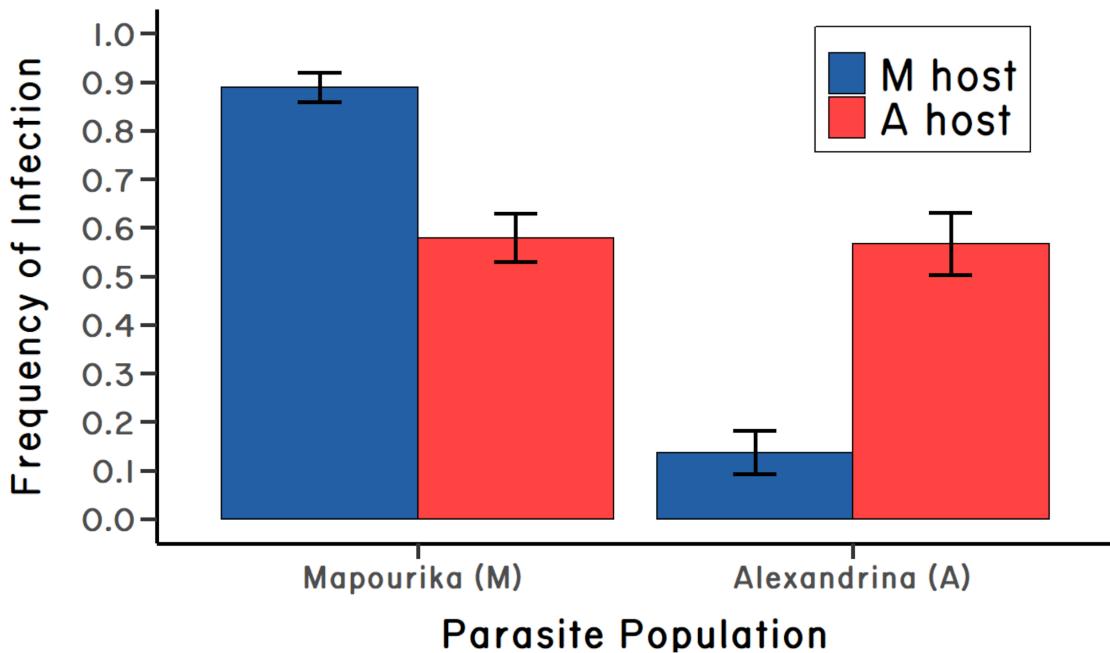


Figure 4.3: Results of the first reciprocal cross-inoculation experiment. The vertical bars show one SE of the mean. Redrawn from Lively (1989).

On the other hand, there were only two lakes in the experiment, so it was unclear if local adaptation was generally true for *Micophallus*. So, I repeated the experiment (Lively 1989). This time I sampled three lakes, all on the west side of the alps. Two of the lakes were less than ten kilometers apart (Lakes Mapourika and Wahapo). The third lake (L. Paringa) was about 100 kilometers south of Lake Mapourika (see map in Lively (1989)). It seemed likely to me that parasite gene flow would be very high between Mapourika and Wahapo, which might reduce or eliminate local adaptation in the parasite. I exposed snails from all three lakes to parasites from each of the three lakes in a fully reciprocal cross-inoculation experiment. Again, the results were very clear: the parasites (following passage through mice) from all three lakes were more infective to host snails from the same lake (Lively 1989). And, to my surprise, the distance between lakes did not matter to the strength of local adaptation (Figure 4.4). Taken together the results from two independent experiments showed strong adaption by parasites to local populations of their snail host. The results also suggested a genetic basis for host resistance and parasite infectivity, which is a crucial assumption of the Red Queen Hypothesis. Finally, the pattern of local parasite adaptation in the snail-trematode system would be found to be very robust in experiments conducted by me and my students after I moved to Indiana University (Figure 4.5).

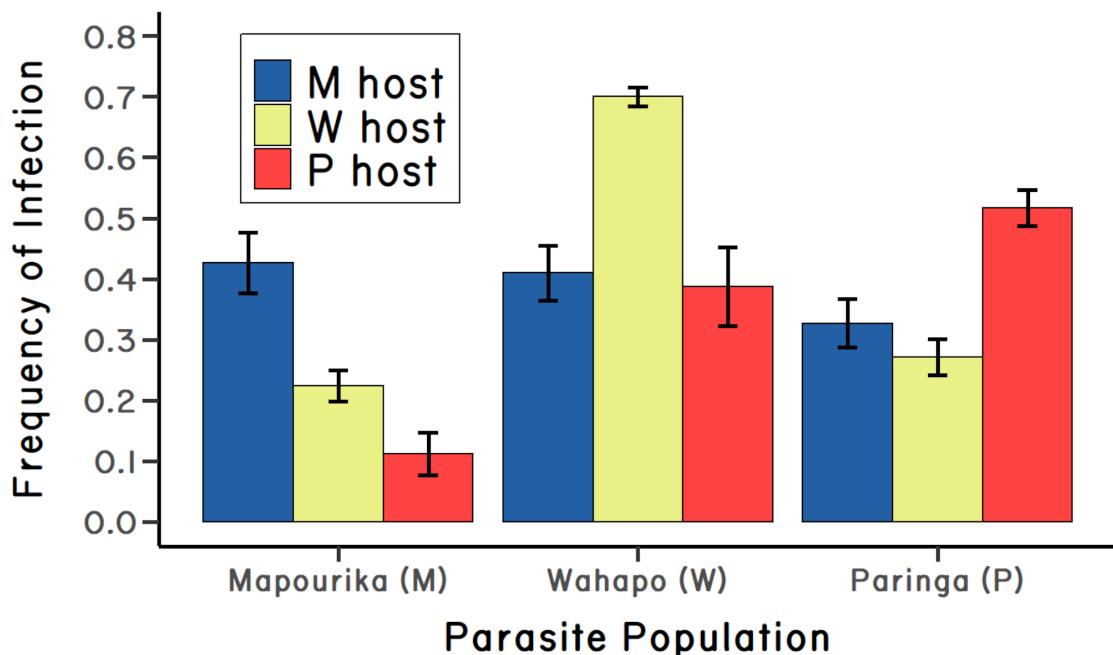


Figure 4.4: Results of the second reciprocal cross-inoculation experiment. Vertical bars show one SE of the mean. Redrawn from Lively (1989).

Does local adaptation by parasites mean that hosts are losing? If so, are hosts maladapted, as often claimed? No and no. The host population is evolving as fast as it can to resist infection by local parasites, and local parasites are tracking the genetic changes in their host populations (with a time lag). This tracking by parasites results in local adaption. In computer simulations, the change in host mean fitness oscillates over time from positive to negative and back. Parasite mean fitness also oscillates from positive to negative, but it is 180 degrees out of phase with the host (Lively 1999b; Lively & Wade 2022). Thus, local parasite adaptation does not necessarily mean that the hosts are losing. Sometimes the host is winning (positive change in mean fitness) and the parasite is losing (negative change in mean fitness), and sometimes the host is losing and the parasite is winning. Over time, the average change in mean fitness for both species is zero.

My early results on local adaptation, along with the results of Parker (1985) and Ebert (1994), convinced me that host-parasite coevolution was interesting, whether or not it could explain sex.² In addition, May and Anderson (1983) had already ignited a general interest in parasites. They showed that, contrary to conventional wisdom, parasites would evolve to maximize their own rates of transmission without any “consideration” for the well-being of their hosts. This work, combined with Hamilton and Zuk’s model of parasite-mediated mate choice, along with Hamilton’s models on parasite-mediated selection for sex, lit up the field (Hamilton 1980; Hamilton & Zuk 1982). Fascinating work by Janice Moore on the evolution of adaptive, parasite-mediated modifications of host behavior piled on (1984). Soon, universities began to advertise for assistant professors working on host-parasite interactions. Then in 1998, Hudson et al. rocked the scientific world with a heroic field experiment, which showed that oscillations in Red Grouse densities were controlled by nematode infections (1998). Parasites were now on the map. An emerging new field called “ecology and evolution of infectious disease” was taking flight.

4.2 Self- / Non-Self-Recognition

In my presentation thus far, I have been assuming that the molecules on the cell surfaces of parasites must mimic host molecules to evade detection. Otherwise, the parasites will be identified as foreign and killed by the host. In other words, there is a self- / non-self-recognition system in hosts, which is determined by a polymorphic set of alleles at one or more loci.

Where did this idea for self- / non-self-recognition come from? I am embarrassed to say that I did not know before writing this chapter, and I am still not exactly sure, but the idea goes back at least to Sir Frank McFarland Burnet, who was cowinner of the 1960 Nobel Prize in Physiology and Medicine (with Sir Peter Medawar). Burnet was reviewing two studies, which showed recognition and rejection of genetically different competitors of the same species (Burnet 1971). The first study was from Hidemiti Oka (1970): “Here I shall explore the possibility that Oka’s (1970) studies of colonial tunicates (*Botryllus*) ... may throw light on primitive types of ‘self and not-self’ recognition from which adaptive immunity may have evolved.” Hidemiti Oka was a Japanese professor of biology in Tokyo. He was following up on a pioneering study by Bancroft (1903), who had shown that fragments from related colonies of a compound ascidian (*Botryllus schlosseri*) readily fused, whereas fragments from unrelated colonies rejected each other. Oka’s goal was to understand the genetic basis for this fusion/rejection. His study suggested that fusion was determined by multiple

²Dieter Ebert showed that parasites of *Daphnia* were locally adapted for both infectivity and transmission, which was a major advance.

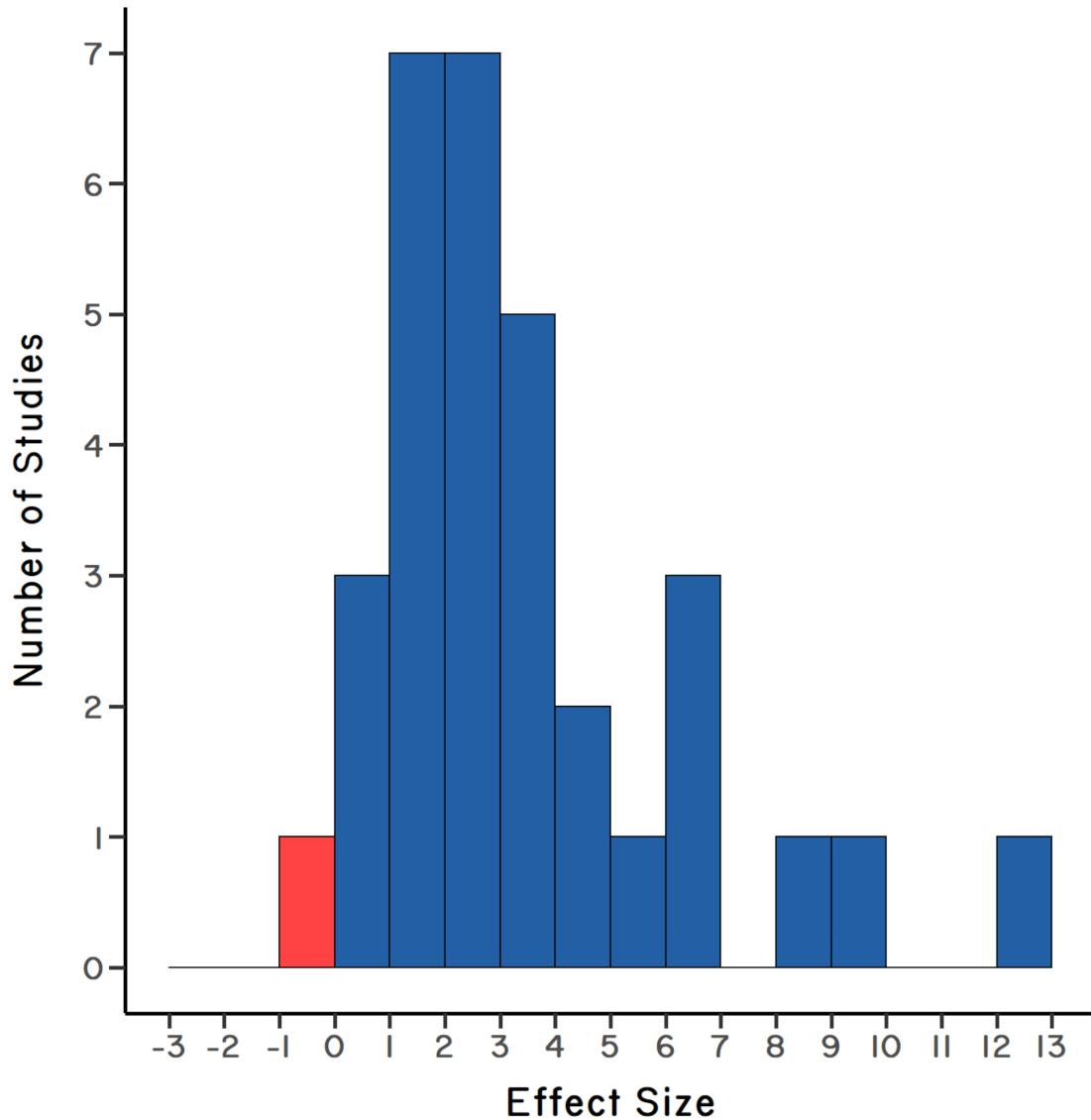


Figure 4.5: Results from a meta-analysis of local adaption experiments. The “effect size” depends on the magnitude of the difference between the proportion of infection in sympatric versus allopatric hosts, where positive values indicate that the parasite is adapted to infecting snails from the local host population. Large effect sizes are indicative of stronger local adaptation by parasites. Positive effect sizes are shown in blue; negative effect sizes are shown in red. A statistical test on the effect sizes showed that, in general, the parasite is strongly adapted to infecting local populations of its host. There were 32 total sympatric/allopatric comparisons. (Redrawn from Lively *et al.* 2004).

alleles (“perhaps several scores”) at a single locus. More specifically, Oka’s results suggested that fusion occurred between different colonies only if they shared at least one allele at this locus.³ To my mind, this was a major finding.

It thus appears that Oka was inspired by Bancroft, and Burnet was inspired by Oka. How does Burnet fit in? Burnet first accepts Oka’s assumption that allorecognition depends on a single highly polymorphic locus (Figure 4.6): “To summarize Oka’s work, it is convenient to accept his assumption, which is validated by much preliminary work, that fusion or rejection between colonies depends on a single locus with many alleles which can be referred to as recognition genes.” Burnet then suggests that this same mechanism could be co-opted as a defense against parasites and that such a mechanism could be the progenitor of the more sophisticated adaptive immune system in vertebrates. Burnet (1971) writes:

It is probably unwise to attempt to imagine the various steps by which such changes could be made. One can foresee a period of great research activity in these fields of tissue fusion and rejection in invertebrates and protochordates during the next decade. Undoubtedly a variety of intriguing phenomena will be uncovered, differing from group to group. Some may be further along the road toward adaptive immunity than the colonial ascidians. Much more extensive comparative studies are called for and in due course analysis of the results should allow a clear evolutionary history to emerge. Whatever form that history eventually takes we can be certain that gene duplication (gene expansion) plays a major part, and that progressive specialization of cell function and phenotypic restriction will be as conspicuous as it is in all other organs and functions.

Wow. In retrospect, Burnet’s “attempt to imagine the various steps” does not seem at all unwise. In any case, he suggests that infection occurs when parasites have alleles that match their host’s genotype. Otherwise, the parasites are killed. This is the logic of what will later be called the “matching alleles model” for infection.

4.3 Summary

1. The most common trematode infection in lake populations of *P. antipodarum* is caused by a larval stage of *Microphallus* sp. (recently renamed to *Atriophallophorus winterbourni*). The trematode has a two-host life cycle (snails and waterfowl).
2. Experimental cross-inoculation experiments showed that *Microphallus* is more infectious to local lake populations of its snail host, *P. antipodarum*, than to remote host populations.
3. These results suggest that some kind of match by the parasite to the host is required for infection. This idea of matching is consistent with the idea of self- / non-self-recognition as the basis for immune defense. The gist of the original idea stems from experimental studies of colony fusion in tunicates.

³In direct contrast, however, Oka found that cross-fertilization did not occur between *Botryllus* gametes that shared the same allele. As Oka noted, this result mirrors the S-allele system in plants: “The ... situation corresponds exactly in its form to the homomorphic self-incompatibility prevailing among angiosperms.”

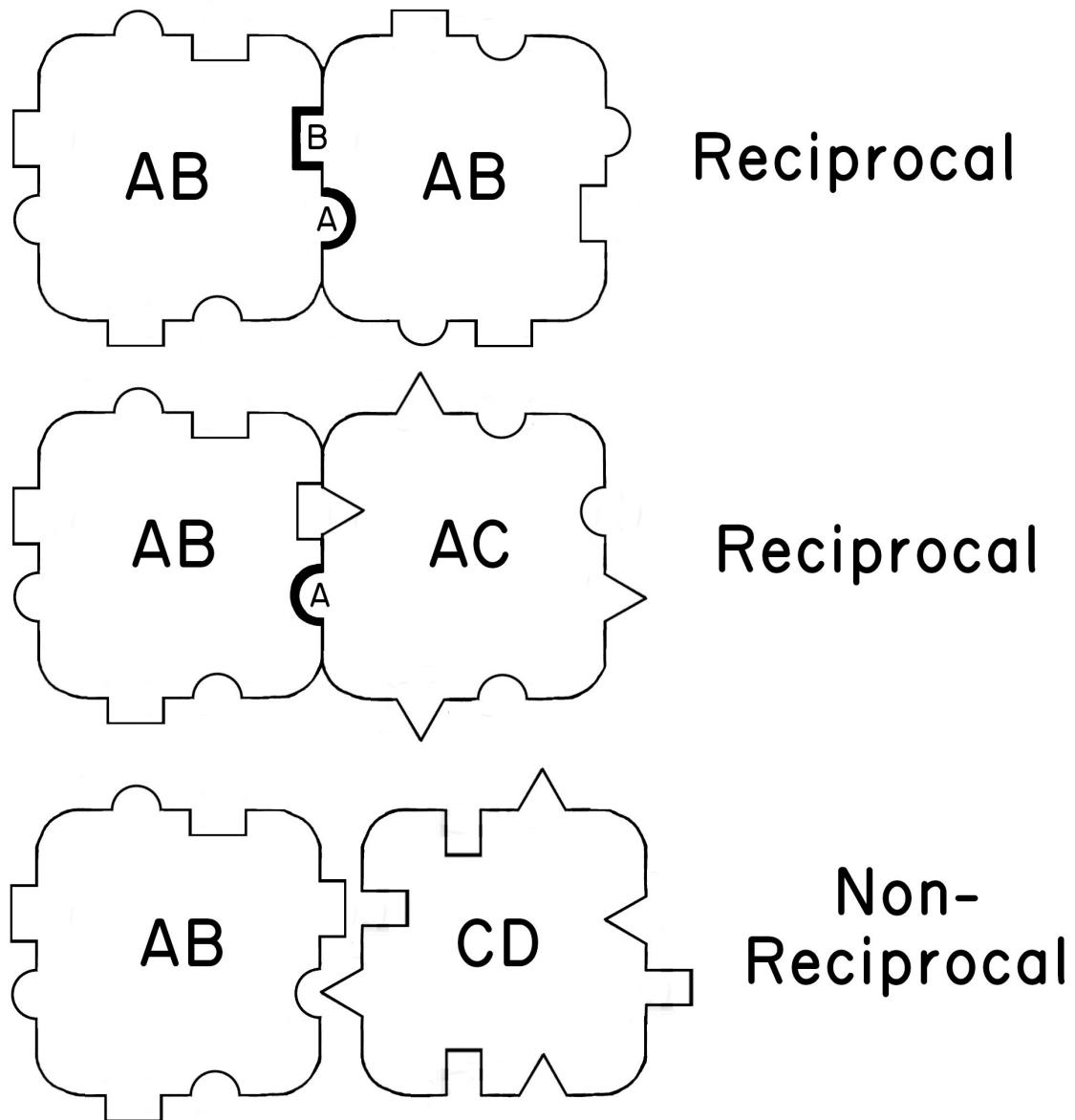
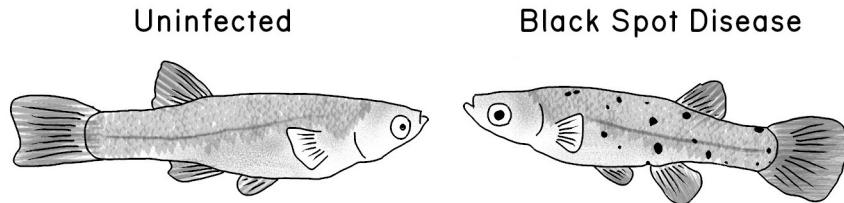


Figure 4.6: A model for self- / non-self-recognition (Burnet 1971; Oka 1970). Cells sharing one or more alleles can rejoin after separation, as the receptors match. In contrast, cells that do not share an allele do not match and will not rejoin. Regions of fusion are shown in heavy lines. Burnet suggested that resistance in host-parasite interactions could have a similar mechanistic framework. Note that Burnet used “reciprocal” for matching cells with at least one matching allele, and “non-reciprocal” for cells in which none of the alleles matched. Redrawn from Burnet (1971) by Zoe M Dinges.

Chapter 5

Gynogenetic Fish



New Zealand felt like home after five years, and we had many good friends and colleagues in Christchurch, especially David Lloyd. David and I talked often about strategic models of natural selection (game theory), of which he was one of the world's leaders. I was particularly influenced by his idea that sexual reproduction, polymorphism, phenotypic plasticity, and hermaphroditism could all be seen under the umbrella of "variation strategies" (Lloyd 1984). Sadly, when Lynda completed her PhD, her visa expired, and we had to leave New Zealand. But where to go?

Lynda was a rising star when she completed her PhD. She landed a post-doc at Rutgers University to work with Tom Meagher, so we moved to New Jersey in January 1989. Once again, Lynda was supporting us. Steven Handel gave me a desk and some space in his lab. Soon afterward, Peter Morin asked me to give a seminar on sex/asex at Rutgers. I knew of Peter's pioneering work in community ecology for which he had received a young investigator's award from the Ecological Society of America (the Mercer Award). I was quite nervous to give a seminar in front of one of my heroes. Another of my heroes, Professor Bob Vrijenhoek, was also in the audience. As described in Section 2.2, Bob was the creative mind behind the Frozen Niche-Variation Hypothesis, and he was well known for his work on sexual and asexual fish (topminnows in the genus *Poeciliopsis*). He was also the director of the Center for Theoretical and Applied Genetics (CTAG) at the New Brunswick campus of Rutgers University, and he was the Editor-in-Chief of the journal *Evolution*, the most prestigious journal in evolutionary biology. After my talk, Bob, Peter, Lynda, and I went out for dinner. Somewhere in the middle of the meal, Bob offered me a post-doc to work with him

at CTAG. I was dumbfounded. But I managed to say yes, “When do I start?” He said, “How about tomorrow?”

For this to make sense, you need to know more about Vrijenhoek’s fish. Like the snails, the fish have coexisting sexual (diploid) and asexual (triploid) forms. The asexual fish, however, were “gynogenetic,” which means that the eggs require fertilization to kick-start embryogenesis. The sneaky eggs, however, do not generally incorporate the sperm’s DNA (review in Vrijenhoek 1998).¹ The outcome is the coexistence of sexual and asexual lineages within the same semi-isolated populations.

Bob had worked on these fish for decades, focusing on small streams in Mexico. He had worked in particular on the coexistence of a sexual form of the fish, *Poeciliopsis monacha*, with two gynogenetic clones, which were interspecific hybrids between *P. monacha* and *P. lucida* (Vrijenhoek 1978, 1979). The triploid clones were independently derived from their sexual ancestors, with two copies of the *monacha* genome and one copy of the *lucida* genome (Schultz 1969). During his studies, Bob had frozen fish for many years from several of his sites. He remembered that some of the fish in his freezer were heavily infected with black-spot disease. The black spots are clearly visible on the body of the fish. The spot itself is caused by trematode larvae that burrow into the fish and encyst (genus *Uvulifer*). The fish’s immune system then coats the cyst with melanin, which turns the cysts black. Bob thought it would be interesting to see if the asexual fish were more infected than the sexuals. The prediction under the Red Queen Hypothesis was that the most common asexual clones would be most infected by black spot disease (Section 5.1).

Bob enlisted the help of one of his PhD students, Clark Craddock. Clark ran the allozyme electrophoresis, which was necessary at the time to tell sexual fish from the two clones. She also helped count the cysts, run the statistics, and write the paper. We found right away that larger fish had more cysts, which makes sense. But we also found that the most common clone, clone 1, had significantly more black spots per unit body length than the sexual fish in Log Pool (Figure 5.1 A & B). In addition, the sexual fish showed greater size-corrected variation in the number of parasitic cysts than the asexual fish, which makes sense if the sexual population contained genetic variation for resistance to infection. So, after correcting for size, the sexual fish were both less infected and showed more variation in infection than the clone 2.² This seemed very promising for the Red Queen.

Similar results were observed in a second pool (Sandal Pool) in which both clones coexisted. In this pool, clone 2 was more common than clone 1, and it was also more infected than clone 1 (Figure 5.2). However, clone 1 was not more infected than the sexual form of *P. monacha*, which showed that clone 1 is not inherently more susceptible to infection (Lively et al. 1990). Taken together, the results suggest that the parasites had evolved to disproportionately attack the most common local clone.

But we had more samples to run. When we examined another pool, the trend reversed: sexual fish were more infected than asexual fish (Figure 5.3 A). We were confused. I remember Clark telling Bob of this new result. He said something like, “Well, that’s science,” and then headed back to his office. He was halfway there when he turned around and asked, “what sample was that?” Clark told him, “Heart Pool, 1983.” Bob got a big smile. Then he told us that, in that sample, the

¹Paternal leakage of DNA in otherwise asexual vertebrate species now seems possible (review in Lampert & Schartl 2010).

²In a follow-up study (using different samples), Weeks (Weeks 1996) did not find some of our significant effects. His sample sizes, however, were small, suggesting that his power to detect differences was low.

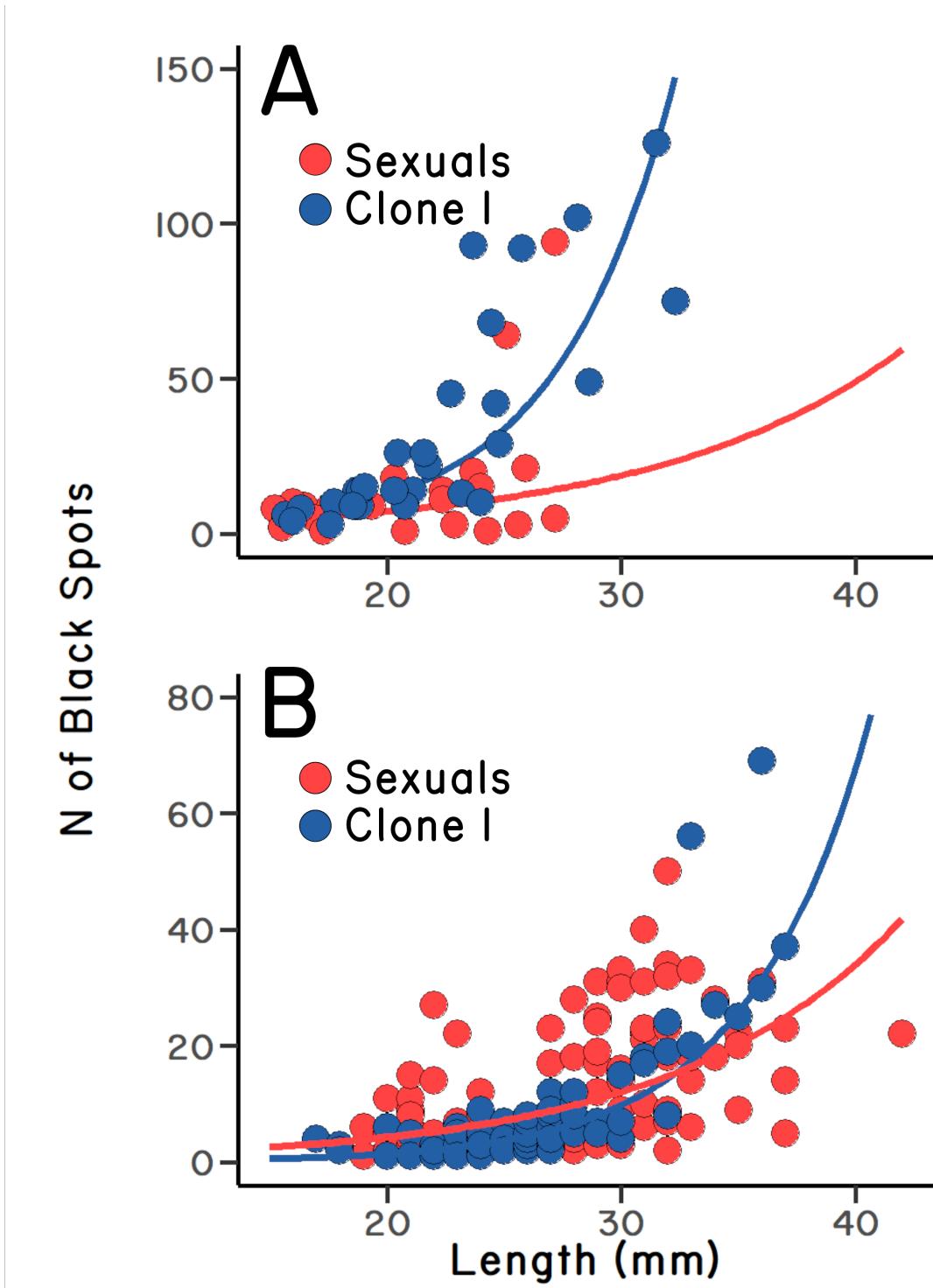


Figure 5.1: Number of trematode larvae per fish in Log Pool. **A.** Log Pool 1978 (number of sexuals = 23, number of clone 1 = 29). **B.** Log Pool 1985 (number of sexuals = 91, number of clone 1 = 81). In both years, the sexual fish showed greater residual variation in infection than clone 1, which hints at an underlying genetic basis for infection. Redrawn from Lively et al. (1990). Note that y axes are the number of trematode larvae plus one.

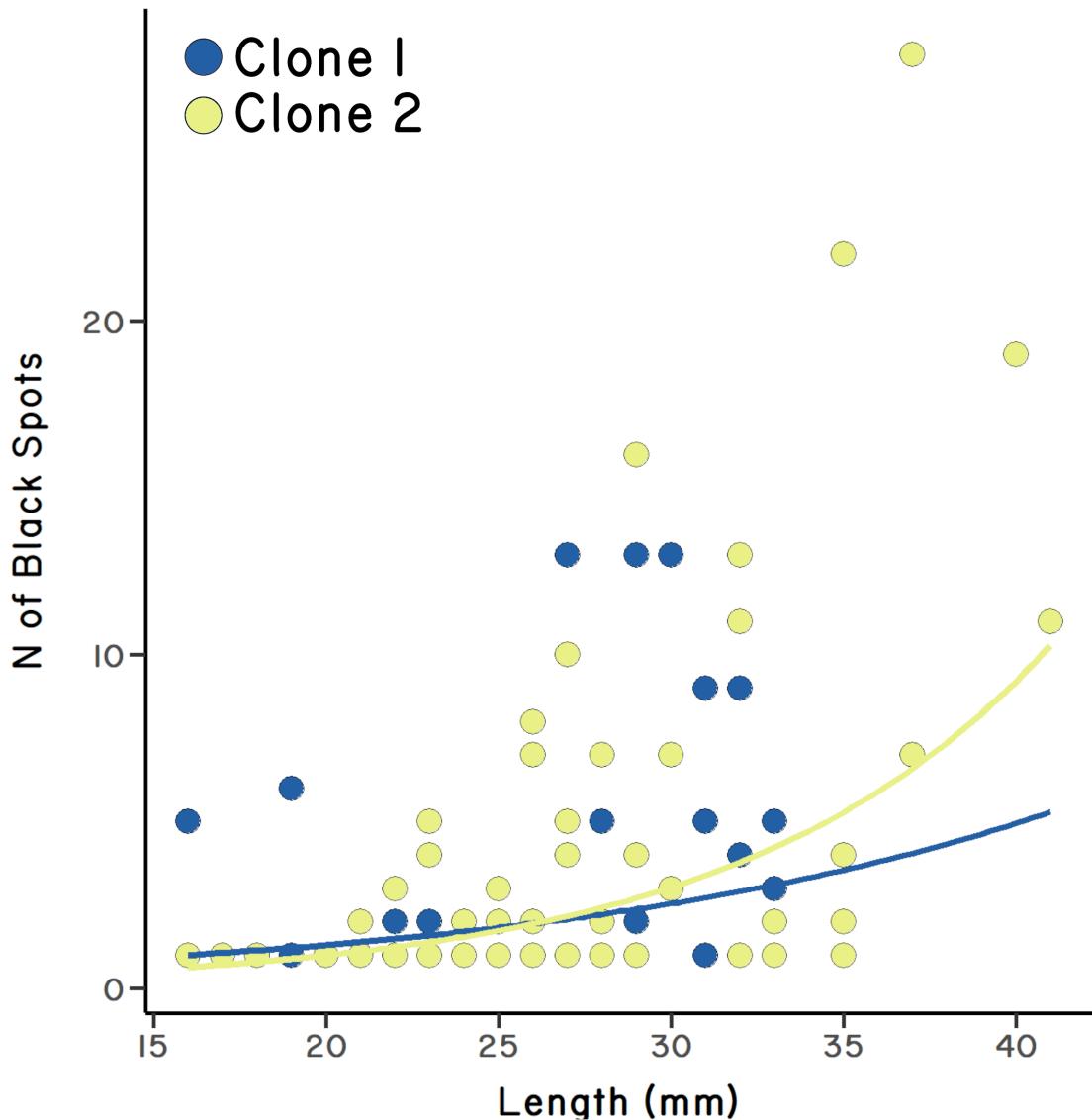


Figure 5.2: Number of trematode larvae infecting clones 1 ($N = 44$) and 2 ($N = 75$) in Sandal Pool 1985. The curve for the sexual population ($N = 138$, not shown) is very similar to the curve for clone 1. Redrawn from Lively et al. (1990).

sexual fish were highly inbred. The population had descended from a small number of founders, and they were homozygous for most loci. So, the sexual fish were more infected in that sample, but they were also genetically depauperate. Under the Red Queen, there is no value to sexual reproduction unless there is genetic variation in the population. On the other hand, the greater level of infection in sexual fish might have been caused by inbreeding depression, which was known for other fitness-related traits (Vrijenhoek & Lerman 1982).

It was an amazing set of results, but there was another twist. Bob had added some fish (in 1983) to the isolated founder population in Heart Pool. His goal was to increase the genetic diversity of the sexual population. After a few years, he resampled the site, and fortunately, he had saved the samples in his freezer from 1985. Clark and I had a look. The pattern had reversed: now the sexual fish were less infected than the asexual fish (Figure 5.3 B). In addition, the size-corrected variance in infection had increased in the sexual fish in just two years. The advantage to outcrossing seemed to depend on genetic diversity.

In summary, the data suggested that the parasites had evolved to infect the most common local host clone in the different pools. They also suggested that sex in genetically diverse host populations results in protection from disease. Both results were consistent with the Red Queen.³ Proof? No. Fascinating? Yes. In any case, looking back, I was very lucky to have had the opportunity to work with Professor Vrijenhoek.

5.1 Appendix: Within Versus Between Populations

It can be a bit confusing, but I think that the predictions of the Red Queen Hypothesis depend on whether one is looking **within versus between populations**. In Chapter 3, I suggested that snail populations having more parasites should be more likely to have some sexual reproduction. Here I am suggesting that asexual fish would be expected to have more parasites. How does that work?

Between populations we would expect to find that host populations without coevolving parasites would evolve to reproduce by parthenogenesis. As such, sex should be positively correlated with infection prevalence. The pattern, however, would be expected to be messy, even in cases where parasites are the major driving force for sex (Lively *et al.* 2021). Nonetheless, the common expectation is that sex should be more common in host populations having a history of strong parasite-mediated selection against common genotypes.

Within populations the most common host genotypes should be more infected, at least periodically. Hence the most common clonal genotypes should be more infected than cross-fertilizing hosts in the sexual population. This might be especially true in cases such as Vrijenhoek's fish discussed here, where parasites may not be virulent enough to drive strong oscillatory dynamics in clone frequencies, and sexual reproduction is most likely maintained by sperm-dependent (psuedogamous)

³It is important to point out that we were not claiming that parasite-mediated selection is maintaining sex in this system. For example, we wrote, “[W]e do not intend to imply from this analysis that the trematode is selecting for the maintenance of sex in these fish.” Niche partitioning and/or the sperm-dependence of the gynogenetic females would most likely ensure the persistence of sexual individuals (Moore & McKay 1971; Schenck & Vrijenhoek 1986). Our claim was simply that parasites had evolved to disproportionately infect the most common clone unless the sexual population was highly inbred.

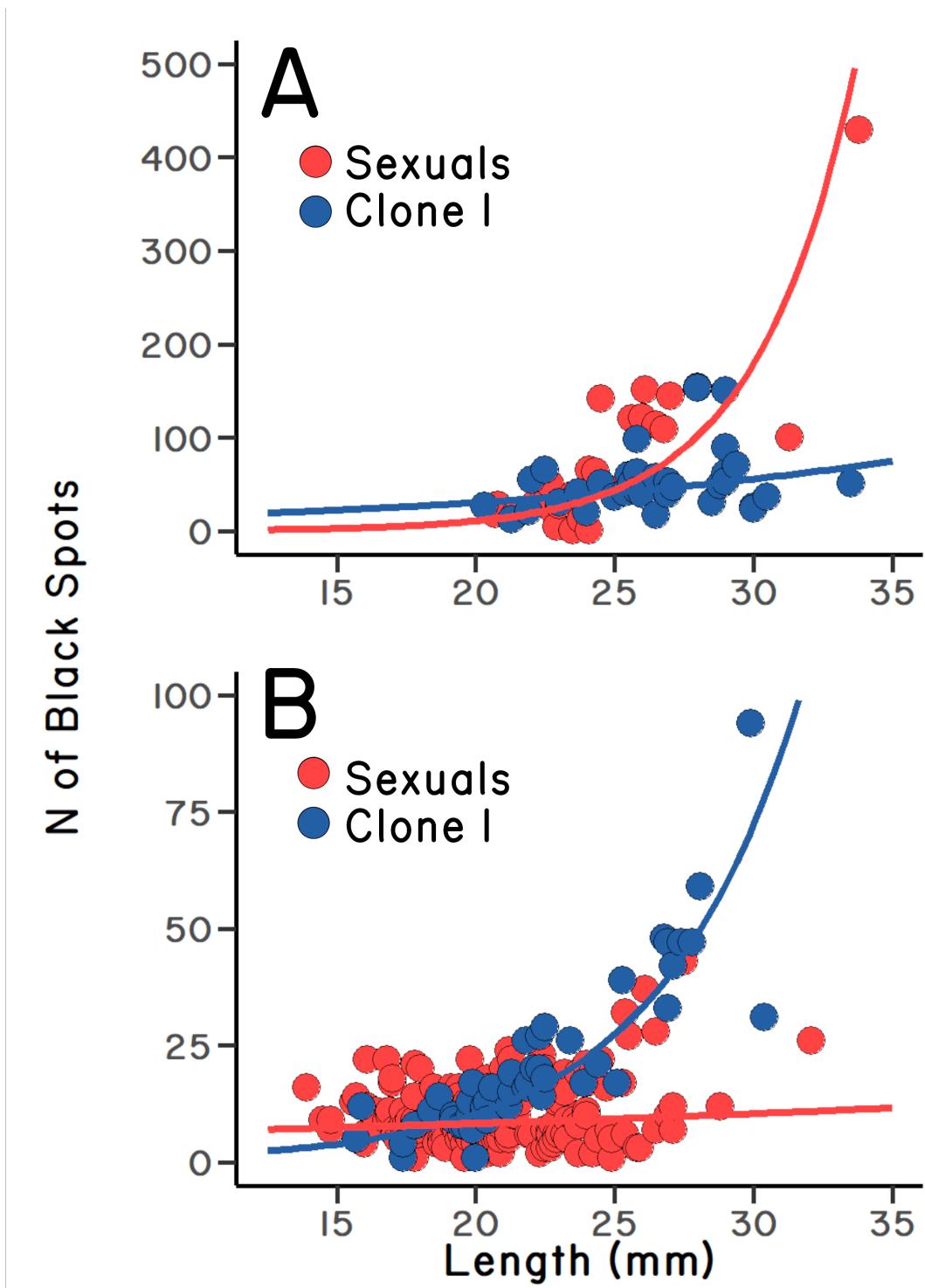


Figure 5.3: Number of trematode larvae infecting fish in Heart Pool. **A (top):** Heart Pool 1983 (number of sexuals = 27; number of clone 1 = 34). The sexual fish in the pool were highly inbred and they were also significantly more infected per unit length than clone 1. The result remained significant after removing the apparent outlier in the sexual population with more than 400 cysts (black spots). The residual variances in the number of cysts were not significantly different between the inbred sexual fish and clone 1. **B (bottom):** Heart Pool 1985 after the infusion of genetic variation into the pool. Here the sexual fish ($N = 171$) were less infected than the coexisting clone ($N = 48$), and they showed significantly greater residual variation for infection than the clone, similar to the results for Log Pool. Redrawn from Lively et al. (1990).

reproduction in the clones (Moore & McKay 1971) and/or by greater niche width in the sexual population (Schenck & Vrijenhoek 1986).

Chapter 6

The Ratchet and the Red Queen



In 1988, Indiana University advertised for an assistant professor in population biology with emphasis on disease ecology. Lynda and I both applied. Happily, we were offered a split position in Biology in which we each got half salary. It may not sound like a good deal, but we were thrilled. It is not easy for a dual-career couple in the same field. We relocated to Bloomington in January 1990, arriving during a cold snap (-20° C). We moved into a university house, but we did not know enough to have the electricity turned on before arrival. Luckily, we still had our down sleeping bags, which we had purchased for field work in the Southern Alps. Aside from the chilly start, moving to Bloomington was the beginning of an academic dream come true.

6.1 The Problem

Since the beginning of my work on sex/asex, there were two things that worried me about the Red Queen Hypothesis. The first of these was pointed out by May and Anderson (1983). This 1983 paper is the same incredible study that launched the wave of studies on the evolution of parasite virulence, but it was also one of the first simulation studies of the Red Queen Hypothesis for sex. May and Anderson concluded that the Red Queen could work, but only if parasites killed their hosts (i.e., they were maximally virulent).¹ So, it seemed to me that the Red Queen could not be a general explanation for sex. It was for this reason that I was biased against the hypothesis when I first started my work in New Zealand. But as May and Anderson pointed out, their model made assumptions that were “not brought down from Mt. Sinai.” They assumed, in particular, that infection was mediated by a single locus with two alleles, giving three genotypes. They also assumed that the clonal population was initiated with all three possible genotypes for resistance. These are critical assumptions, as we will see in Part Two (or see Lively 2018).

The second problem was that parasites do not select for sex per se. They only select against common genotypes. This means that once parasites drive a common clone down to a rare frequency, it should become favored by selection. Barring loss of the clone by chance in small populations, the clone should increase in frequency, eventually leading to oscillations over time. So, while parasites might prevent the fixation of the clone in the short term, they do not eliminate it. Now here is the problem. What if a second clone, with a different genotype, arises in the population? It should also spread when rare. So should any new clone. Given that parasites are simply a source of frequency-dependent selection, parasite-mediated selection should lead to the accumulation of different clonal genotypes (Lively & Howard 1994).² It seemed obvious that, if clonal diversity became sufficiently high, the diverse clonal population would eliminate the sexual population. Hence the Red Queen did not seem stable in the face of repeated mutation to asexual reproduction. I began to think that combining alternative hypotheses might be useful. I turned first to Muller’s ratchet.

6.2 Muller’s Ratchet

Herman J. Muller was a prize-winning geneticist. He won the Nobel Prize in Medicine and Physiology just one year after moving to Indiana University in 1945. In the early 1960s, Muller was invited to write an introductory paper for a new journal. The editor made an effort to acknowledge Muller in the preface to this first issue (Sobels 1964): “We are particularly honored that we can start the journal with a paper by Dr. H. J. Muller.” In this inaugural paper, Muller wrote a bomb sentence (1964): “[w]e find that an asexual population incorporates a kind of ratchet mechanism, such that it can never get to contain, in any of its lines, a load of mutations smaller than that already existing in its at present least-loaded lines.” In other words, obligately asexual populations

¹May and Anderson, for example, state, “Our studies, in which the epidemiological details of the parasite–host interactions are treated more explicitly than in Hamilton’s work, make this [the parasite] answer to the problem of sex (Ghiselin 1974; Maynard Smith 1978; Williams 1975) less likely.”

²In a computer simulation, a sexual population with eight possible genotypes (three locus haploid model with two alleles each) was rapidly replaced by two randomly selected clonal genotypes. The first clone was introduced at time one, and it began oscillating with the sexual population. The second clone was introduced at time 100. It began oscillating out of phase with the first clone. The sexual population was driven to extinction by generation 150 (Lively & Howard 1994). Thus, sexual reproduction may not be stable to invasion and replacement by a diverse clonal population.

should accumulate deleterious mutations over time. A decade later, Joe Felsenstein named the idea “Muller’s ratchet” (1974), and he pointed to the probable importance of the ratchet in population genetics.³ The concepts underlying the idea are not especially intuitive, but I will try to explain the gist of it. First, we must ask, what is a clone?

I have been using “clone” so far to describe a group of genetically identical descendants from a single asexual individual. But Muller knew that this was not strictly true because mutation happens. Thus, as any new clone spreads in a population, mutations accumulate, leading to variation among individuals in the number of mutations (Figure 6.1). It must be true then that there is a group of individuals within the clone that have the fewest mutations. Muller called this the “least-loaded class.” Here is Muller’s insight. Given that the least-loaded class in a finite population might be a handful of individuals, the least-loaded (most fit) class could be lost by chance. How would that happen? Two ways. First, the members of the least-loaded class (“LLC”) could be lost by bad luck. Maybe all five of members of the LLC were washed away by a flood, or anything related to being in the wrong place at the wrong time. Second, the members of the LLC might produce offspring with one (or more) new mutations. Clearly, the two options are not mutually exclusive. The point is the least-loaded class can be lost. This means that the ratchet clicks towards a greater mean number of mutations in an asexual line.

My students will immediately engage, “Okay, but the most-loaded class could also be lost for the same reason.” Yes, that is correct. But the most-loaded class can be restored by new mutations in the second most-loaded class. In contrast, the LLC can only be restored by back mutation, which has a very low probability of occurrence. Hence, the mean number of mutations in a clonal lineage is expected to increase over time, thereby decreasing mean fitness and eroding the advantage to asexual reproduction.

The ratchet, however, takes a long time to work, especially in large populations where genetic drift is less problematic. As such, a clone would likely outcompete and eliminate the coexisting sexual population before the ratchet drives the clone to extinction. Hence, Muller’s ratchet does not seem to be a viable stand-alone explanation for the persistence of obligately sexual populations. But what if there were a force that periodically reduced the number of clonal individuals? That should increase the rate of mutation accumulation by genetic drift in the asexual lineage. Hopefully, you can see where this is going.

6.3 Synergistic Ideas? The Ratchet and the Red Queen

Here is the idea. Parasite-mediated selection against common genotypes might prevent the fixation of a clone in the short term. Parasites could also drive clones through periodic bottlenecks, which would speed up the rate at which the ratchet clicks. The ratchet could then gradually reduce the reproductive advantage of asexual reproduction. Eventually the clone would be eliminated, not by parasites, but by a parasite-driven ratchet. Perhaps the ratchet could eliminate different clonal lineages as quickly as they were generated by mutation in the sexual population.

³From Felsenstein (1974): “I will not attempt here to predict from theory the quantitative effect of the ratchet mechanism. Involving natural selection, mutation, and genetic drift at many linked loci, the problem poses enormous difficulties for the application of population genetics theory. But the possible significance of the phenomenon makes it important that some theoretical treatment should be attempted. The ratchet mechanism has been unjustly ignored by theoretical population genetics.”

My first PhD student at Indiana University was Steve Howard, who transferred in from another lab. Early on, we had many discussions about our experiences as construction workers and our fondness for characters in John Steinbeck's books. We also began to expand on the possibility of synergism between the ratchet and the Red Queen. During one of our sessions, Steve (in a whimsical moment) said that he could have a solution in the morning. But it was not an overnight problem to solve, as we both soon realized. The solution required an individual-based computer simulation, which was not common at that time (Judson 1994). By that I mean that Steve had to write a simulation that kept track of every individual in the population, including whether it became infected, and whether it produced offspring with one or more new mutations. Steve is a locked-on theoretician. He could not sleep during the construction of his model, and he would sometimes call me in the middle of the night. First, he had to show that the model would converge on analytical solutions for the number of mutations at equilibrium. This equilibrium is called "mutation-selection balance," which occurs when the input of mutations is exactly cancelled out by the elimination of mutations by natural selection (Section 6.5). But what is the analytical solution?

As in any model, there are assumptions involved. For starters, let's assume that the proportional reduction in fitness caused by each new mutation is the same as for all previous mutations (independent effects). Therefore, the fitness of an individual with k mutations is given by $(1 - s)^k$ where s gives the selection against each mutation. Kimura and Maruyama (1966) showed that the number of mutations at mutation-selection balance is equal to U/s , where U is the expected number of new mutations in offspring. Further, they showed that mean fitness at mutation-selection balance is equal to e^{-U} , assuming that selection is weak (Figure 6.1). Following Kimura and Maruyama's results, John Haigh showed further that the number of individuals in the least-loaded class (n_0) at mutation-selection balance is: $n_0 = Ne^{-U/s}$ where N is the total population size (Haigh 1978). Keep in mind that the number of individuals in the least-loaded class (n_0) is an especially important value, because the smaller the number, the easier it is to lose it by drift, resulting in one click of the ratchet. Haigh also showed that, once the ratchet clicks, the original (Poisson) distribution of mutations is reset, where the mean of the distribution is increased by one (Figure 6.2). Critically, Haigh's result suggests that n_0 can be fewer than 10 individuals, even for very large population sizes. The ratchet seems unavoidable.

Happily, Steve's simulation converged on the analytically derived values for the mean number of mutations and the mean fitness at mutation-selection balance. Now for the more difficult part. Does host-parasite coevolution accelerate the accumulation of mutations in clonal lineages? Does the combination of the ratchet and the Red Queen lead to extinction of the clone before it eliminates its sexual competitors? Note that the simulation made the conservative assumption that infected individuals in the most-loaded class had the same fitness as infected individuals in the LLC. In other words, infection was not more severe in individuals having more mutations.

Steve's simulations showed that, in the absence of parasites, an initially rare clone went to fixation in fewer than 50 generations, thereby driving the sexual population extinct (Howard & Lively 1994b).⁴ However, after about 500 generations, the clone also went extinct due to the accumulation of mutations via the ratchet. Hence, the ratchet was sufficient to take out the clone, but not before the clone replaced the entire sexual population. In the presence of parasites, but without

⁴After the proofs were corrected and returned, the shading was washed out in Figures 1 and 2. Even worse, the panels were reversed for Figure 3. The corrected figures were reprinted in Howard and Lively (1994a).

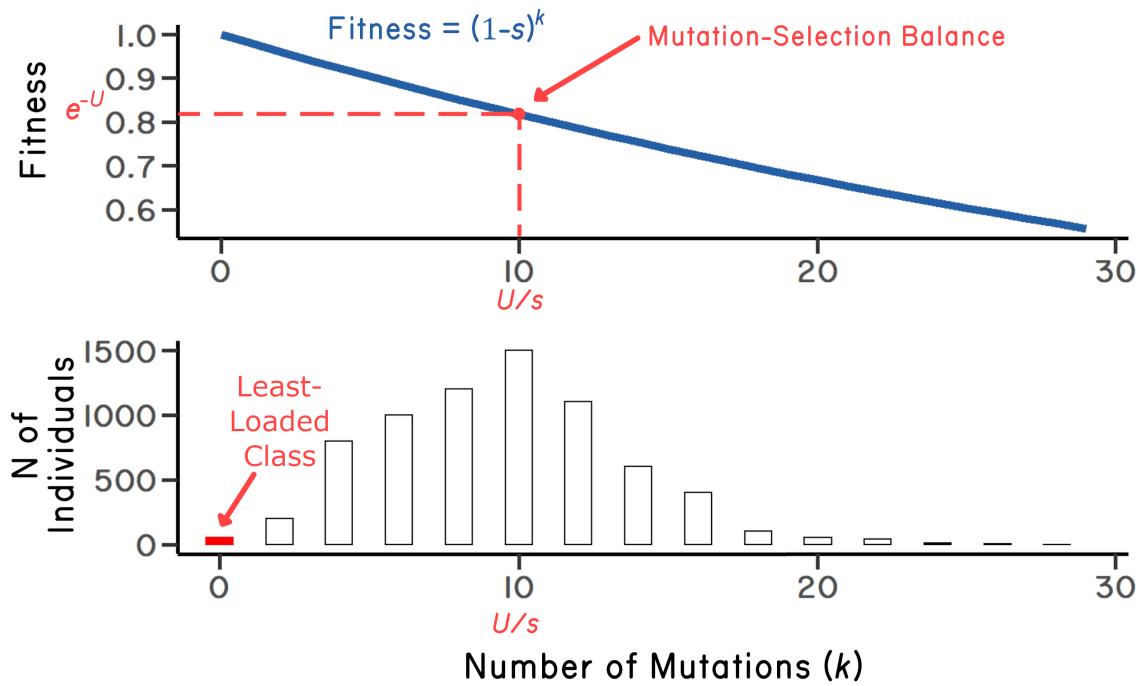


Figure 6.1: **A.** Fitness as a function of the number of mutations assuming independent effects. **B.** The distribution of mutations at mutation-selection balance. Note that the number of individuals in the least-loaded class is $Ne^{-U/s}$, which can be a small number. The ratchet clicks whenever the least-loaded class is lost by chance.

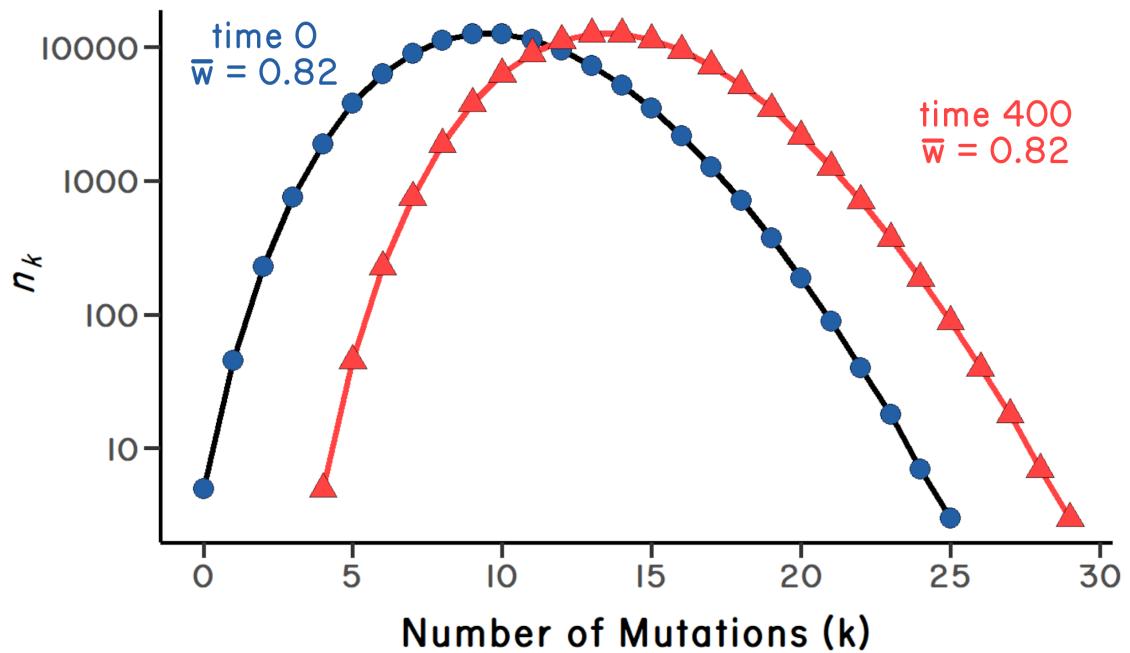


Figure 6.2: The distribution of mutations at two time points, following Haigh's (1978) simulation results for $N = 100,000$, $s = 0.02$, and $U = 0.2$. The blue line shows the distribution of mutational classes before the operation of the ratchet. The red line shows the distribution after 400 generations, following four clicks of the ratchet. The number of individuals in the LLC is five at both time points. Mean fitness (\bar{w}) is relative to individuals with zero mutations.

the ratchet, the clone also rapidly replaced the sexual subpopulation, and the clone's descendants remained at carrying capacity for the duration of the simulation (Figure 6.3).

By contrast, when parasites were combined with the ratchet, sexual reproduction was initially invaded by the clone, but the clone did not replace the sexuals. How does that work? The clone was initiated with a small number of individuals ($N = 20$) at mutation-selection balance. The clone then increased when rare, but as the clone spread in the population, the ratchet was already working to reduce the two-fold cost of males (see Chapter 1). In addition, as the clone became common, the parasite population rapidly evolved to infect it. This combination of the ratchet and parasite-mediated frequency-dependent selection prevented the clone from fixing in the short term. The clone then began to oscillate in frequency over time. But every time the clone was driven to low frequency, the number of individuals in the LLC decreased, thereby allowing for a more rapid operation of the ratchet. Notably, over the period of several oscillations, the clone tended to be driven to lower frequencies each time. So as the ratchet erodes the cost of males, the clone was driven to a lower frequency during successive oscillations, which fed back to fuel the ratchet. The clone is toast. Eventually the clone undergoes a mutational meltdown and goes extinct (Lynch & Gabriel 1990).⁵ This example provides a proof of concept that host-parasite coevolution can work in a synergistic way with Muller's ratchet to prevent fixation of the clone in the short term (<20 generations) and to ensure the elimination of the clone in the longer term.

To get a better feeling of the parameter space over which the ratchet and the Red Queen could work to select for sex over the long term, Steve explored different combinations of mutation rate, selection against mutation, parasite virulence, and parasite transmission. In the absence of mutation, the results showed that sexual reproduction was evolutionarily stable only when parasites were both extremely virulent and highly transmissible (Figure 6.4). This result was consistent with the model of May and Anderson (1983). Sexuals and asexuals coexisted where parasite virulence and transmission were both high, but not at maximum values (Figure 6.4). Finally, asexual reproduction replaced sexual reproduction when parasites had low levels of virulence and/or transmission.

Now, what if we add in mutation? Steve's results suggested that for genome-wide mutation rates of $U = 0.5$ to 1.0 , sexual reproduction was stable to replacement by asexual reproduction, even when parasites **were only moderately virulent**.⁶ This surprised us! One of the major difficulties for the Red Queen had been that May and Anderson's (1983) results suggest that parasites had to kill or sterilize infected hosts to provide sufficiently strong selection for cross-fertilization. Steve's new results suggested that, in combination with the ratchet, parasites did have to generate such strong selection against infected individuals (Figure 6.5). When we started out, we had not imagined that the synergism between the ratchet and the Red Queen could be so powerful.⁷

The potential for synergism between antagonistic coevolution and mutation accumulation later became the subject of a target review in 1999, headed up by Stuart West (1999). Stu was a post-

⁵Mutational meltdown in clones occurs when their intrinsic birth rates are near one, meaning that the females are just barely replacing themselves. This then keeps the clonal population small, which also keeps the least-loaded class small, thereby aiding the ratchet. Once the intrinsic birth rate drops below one, the clone will go extinct.

⁶"Virulence" is defined here as the effect that infection has on host fitness. For example, a virulence value of 1.0 indicates that infection kills or sterilizes the host. A virulence of 0.1 indicates that infection reduces host fitness by 10%.

⁷Steve followed this initial study with a simulation study of mutation accumulation in a Red Queen world but changing the assumption from independent effects of mutations to synergistic effects of mutations (Howard & Lively 1998). The results were similar, provided the clonal population has not come into mutation-selection balance.

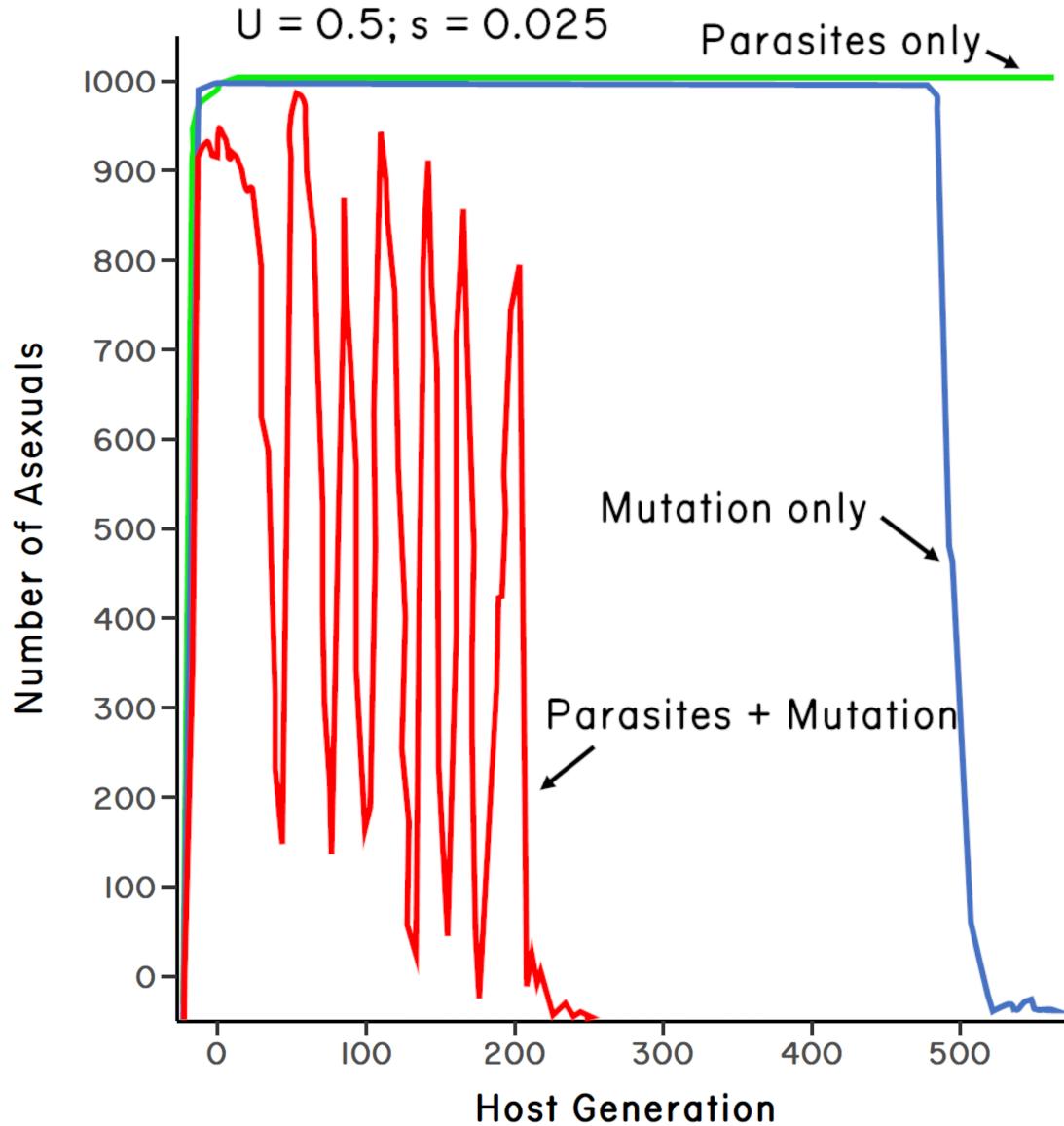


Figure 6.3: Representative simulation results. The green line shows a simulation for hosts infected with coevolving parasites, but in the absence of deleterious mutations. Virulence and transmission were both moderate ($= 0.5$). Under these conditions, the sexual hosts were eliminated by the clone. The blue line shows a case without parasites in which mutations occur with a probability of 0.5 per genome per generation ($U = 0.5$), and selection against mutation is $s = 0.025$. Again, the clone goes to fixation, but it is later eliminated by Muller's ratchet. The red line shows a case where both mutations and coevolving parasites were included. Here, the clone did not replace the sexual population but rather oscillated in frequency, which led to more rapid mutation accumulation and elimination of the clone. Redrawn from Howard and Lively (1994a).

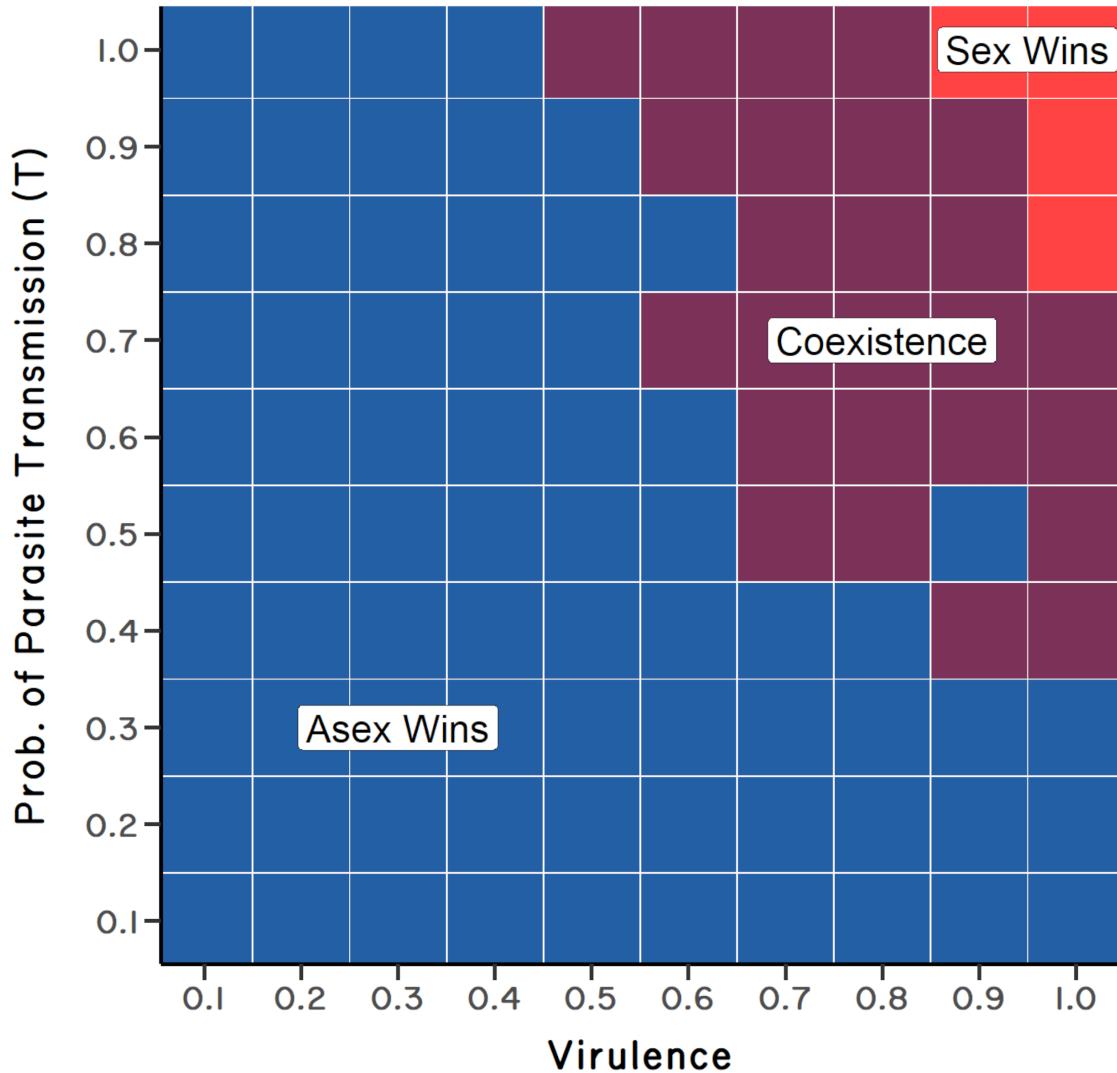


Figure 6.4: Parameter space showing regions where sexual reproduction persists in the face of competition with a single clone in the absence of mutation. Note that sexual reproduction only wins outright when virulence is at or near its maximum value of one and transmission is also very high. Asexual females replace sexuals at low levels of transmission and virulence. Finally, there is an intermediate zone on the virulence-transmission axis where sexual and asexual females coexist. Redrawn from Howard and Lively (1994a).

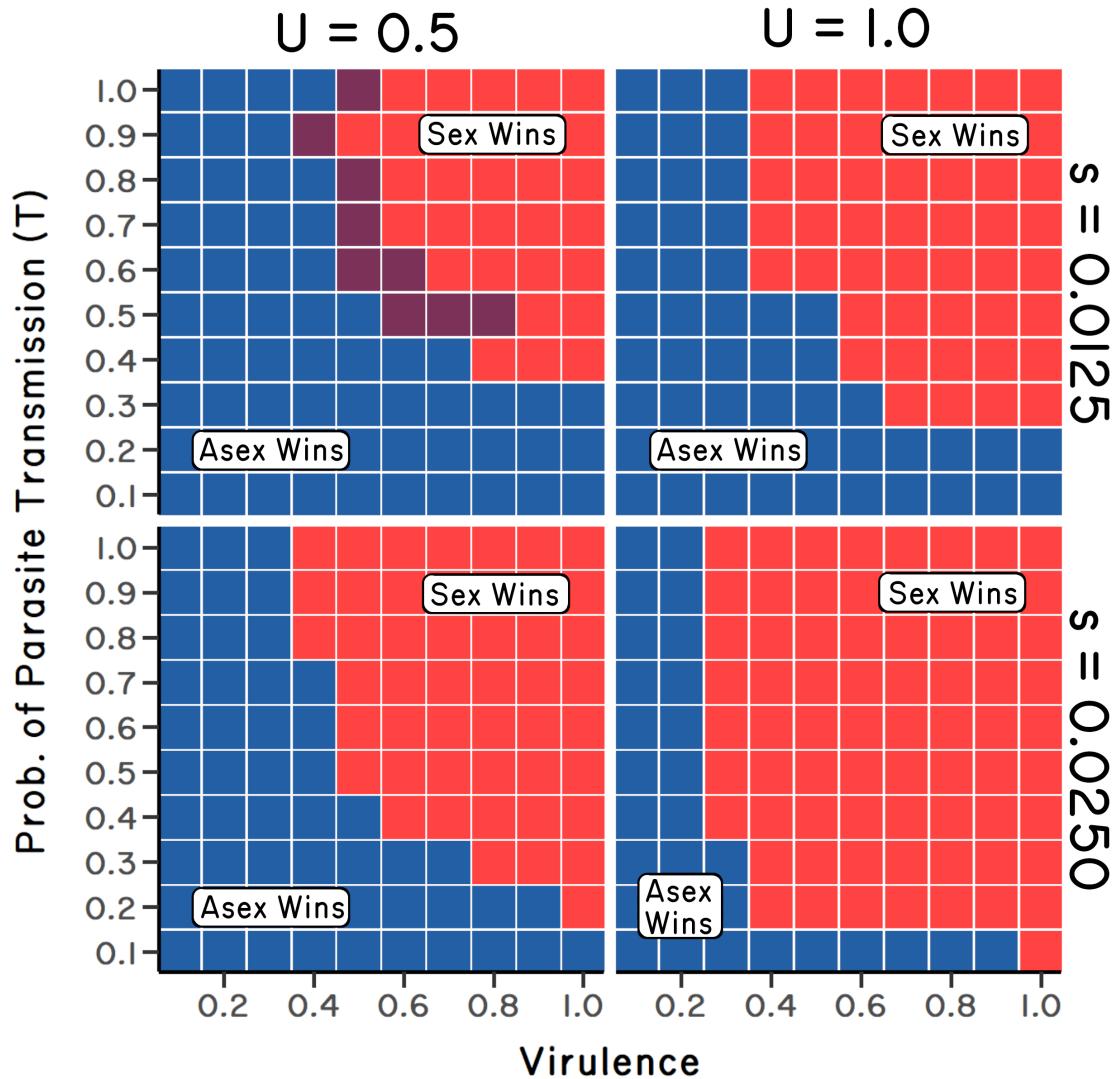


Figure 6.5: Parameter space showing regions where sexual reproduction persists in the face of competition with a single clone in the presence of mutation. In comparison to the case without mutation (Figure 6.4), sexual reproduction is stable over a much wider range of values for transmission and virulence. The zone of coexistence is also greatly reduced (purple squares). Redrawn from Howard and Lively (1994a).

doc in Andrew Read's lab in Edinburgh while I was there as a sabbatical visitor in the lab. But the whole thing originally started at a meeting we all attended at the Max Planck Institute in Seewiesen, Germany. It was an amazing gathering on the evolution of sex, organized by Nico Michiels, with an incredible mix of faculty, post-docs, and students. I presented some of the snail data along with the results of Howard and Lively (1994b) to a rather mixed reaction. To my mind, it seemed that the students and post-docs (including Stu) liked the idea of combining hypotheses, but at least one of the more established members in the field saw it as an attempt by hippies to make everyone happy.⁸ In any case, Stu expanded on the basic idea back in Edinburgh, and he convinced Andrew and me to help him craft it as a target review for the *Journal of Evolutionary Biology*. I was very reluctant, as several key researchers in the field would be asked to publish their thoughts on the matter, which I knew were unlikely to be uniformly positive. In the end, our paper was published—along with over a dozen commentaries (see vol. 12, issue 6). The commentaries were more positive on average than I expected, but mainly it was interesting to see the diversity of thought by some of the top biologists studying sex and recombination at the time.

My work with Steve Howard on synergism between the ratchet and the Red Queen led me to rethink my views on Strong Inference, as discussed in Chapter 3, where the goal is to force competing hypotheses to make different predictions before getting the data. But what if the answer is some combination, or even synergism, between hypotheses? It could be that forcing predictions could result in the rejection of all alternatives, when in fact two or more hypotheses were partially true. And if two hypotheses are strongly synergistic, would it be appropriate to claim that one was more important? In studying this problem, I found an excellent article contrasting Platt's strong inference with Chamberlin's method of multiple working hypotheses (Elliott & Brook 2007). Elliott and Brook state that the two methods are often treated as the same idea (of which I was guilty in Chapter 3). But they are not the same. Platt's paper (which drew heavily from Chamberlin) focused on designing programs that would falsify all but one of the alternatives, whereas Chamberlin allowed for combinations, and even synergism, between competing hypotheses. It now seems to me that Chamberlin's original (1890) paper better describes the best way forward with respect to the problem of sex.

6.3.1 What about parasites?

One of the major patterns of sex/asex was pointed out by Graham Bell. He found that parasitic species were much more likely to be outcrossing than their free-living relatives (Bell 1982). This finding was emphatically supported by a formal phylogenetic study of free-living versus parasitic nematodes (Gibson & Fuentes 2015). However, much of the theoretical focus for sex/asex has focused on hosts. What about parasites? If host-parasite coevolution can contribute to selection for sexual reproduction in hosts, does it also feedback to select for sex in parasites? If so, is it sufficient? Steve Howard was one of the first theoreticians to address these questions along with Alison Galvani and Katrina Lythgoe (Galvani *et al.* 2003; Lythgoe 2000). Steve's results showed that sexual populations of obligate parasites could be invaded and replaced by a diverse population of clonal parasite genotypes. More specifically, repeated mutation to asexual reproduction in the parasite population led to a diverse clonal population, which eventually replaced the ancestral sexual population. However, the ratchet, in combination with Red Queen dynamics, could lead to the elimination of clones and the long-term maintenance of sexual parasite populations (Howard &

⁸I heard this kind of thing called “group-hug pluralism” at a meeting of philosophers in Berlin in 2022. In any case, our fusion of the ratchet and the Red Queen was based on logic rather than any sort of craving for hugs.

Lively 2002). Hence, the results for parasites mirror those found for hosts, except that the ratchet worked more rapidly in obligate parasites, as selection is stronger, giving rise to more extreme oscillations during Red Queen dynamics. It is still unknown whether the ratchet and the Red Queen work synergistically to select for sex in either parasites or hosts.⁹ But it seems like a sensible possibility, especially where both host and parasite genetic diversity is very high, host populations are finite, and parasites rarely coinfect the same host individual. It is also possible, of course, that neither coevolution nor mutation accumulation is required. More empirical and theoretical work is required.

6.4 Summary

1. The Red Queen Hypothesis is a potentially general way of explaining why clonal lineages don't rapidly replace sexual competitors in the short term.
2. But any source of frequency-dependent selection (such as parasites or niche competition) would seem insufficient by itself to eliminate clones when rare. However, the elimination of rare clones could be aided by either demographic stochasticity in finite populations and/or by Muller's ratchet.
3. In the case of Muller's ratchet, parasite-mediated frequency-dependent selection could facilitate the ratchet-like mechanism by periodically reducing the size of the clonal population, thereby increasing the rate of mutation accumulation.
4. The ratchet/Red Queen idea is very difficult to test, but data for *P. antipodarum* suggest that long-lived clonal lineages are most likely in populations that are relatively parasite free (Neiman *et al.* 2005).

6.5 Appendix: Down the Ratchet Hole

Suppose the probability of a new mutation in offspring is 0.5. Clearly, it would not make sense to say that every offspring acquires one half of one mutation. But it would make sense to say that offspring have a Poisson distribution of new mutations. Under a Poisson distribution, the frequency of individuals with k new mutations is given by:

$$f_k = \frac{e^{-U} U^k}{k!}$$

where U is the probability of a new mutation per generation. Under this formulation, the frequency of offspring that contain no new mutations is given by:

$$f_0 = e^{-U}$$

⁹Professor Hamilton told me at a meeting in London that he thought combining the ratchet and the Red Queen made sense, but that he did not think the ratchet was a necessary addition. See also the dissertation work by Olivia Judson for a detailed theoretical study of coexistence between sexuals and asexuals in a metapopulation (Judson 1997).

Suppose a clonal population begins with a single individual with zero mutations ($k = 0$ and $w_0 = 1$). As above, let all future offspring acquire an average of U additional mutations per generation. The lineage would gain mutations over time, until the input of mutations is equal to the loss of mutations due to selection. At this point in time, the clonal population is at mutation-selection balance. Kimura and Maruyama (1966) showed that the average number of mutations in a clonal lineage at mutation-selection balance is equal to U/s , where s is the selection coefficient against each mutation. They also showed that the mean fitness at this balance (assuming that s is small) is:

$$\hat{w} = e^{-U}$$

Hence, population mean fitness at equilibrium is expected to be equal to the expected frequency of zero new mutations in offspring.

In an infinite population, we would expect the mean fitness to remain at this equilibrium value. But populations are finite, which leads to Muller's ratchet. John Haigh constructed the first model to deeply explore the ratchet (1978). He first assumed that each deleterious mutation results in the same proportional reduction in fitness as all previous mutations. Let s be the selection coefficient against each mutation. Under Haigh's assumption, an individual with zero mutations would have a relative fitness of 1, while an individual with one mutation would have a relative fitness of $(1-s)$, and an individual with two mutations would have a relative fitness of $(1-s)(1-s)$. More generally, an individual with k mutations would have a relative fitness of:

$$w_k = (1-s)^k$$

Haigh assumed that the number of *individuals* having k mutations (n_k) at mutation-selection balance also follow a Poisson distribution, such that

$$n_k = \frac{n_0 \left(\frac{U}{s}\right)^k}{k!}$$

In this expression, n_0 is the number of individuals with zero mutations, which is the least-loaded class. How many individuals in the least-loaded class? Let N be the total number of individuals in the clonal population. Under a Poisson distribution for mutational load, the number of individuals in the least-loaded class is

$$n_0 = Ne^{-U/s}$$

where $e^{-U/s}$ is the frequency of individuals in the zero class. This means that the LLC can be quite small, even in large clonal populations. For example, let $N = 100,000$, let $s = 0.02$, and let $U = 0.2$. Plugging these values into the solution for n_0 we find that only five individuals would be in the LLC at mutation-selection balance. Such a small group is at risk of loss by genetic drift.

Haigh ran simulations to study the loss of the LLC, and the effect of this loss on the distribution of mutational classes. He found that following the loss of the LLC, the entire distribution shifted to

a greater mean number of mutations, but the shape of the distribution remained constant. Hence, after one click of the ratchet, the LLC still had about five individuals, but now the LLC had one additional mutation. The mean number of mutations had also increased by one.

Glossary

Short definitions of terms as used in this book. These definitions do not include all possible nuances.

Carrying capacity: The population density at which females have just enough food to replace themselves. Sexual females must make two offspring to replace themselves (assuming a 1:1 sex ratio), while asexual females must only produce one offspring. Hence, asexuals should have higher carrying capacities, as shown in Figure 1.2.

Cost of males: The reduction in the per-capita growth rate of sexual populations due to the production of males. The cost of males is the appropriate cost for considering sexual subpopulations in competition with obligately asexual subpopulations.

Cost of meiosis: The reduction in relatedness between mother and offspring due to outcrossing. The cost of meiosis is the appropriate cost for considering the spread of alleles that induce self-fertilization.

Clone: A lineage of parthenogenetic females descended from the same asexual female. Members of the same clone may have small genetic differences, which accumulate by mutation over time.

Cross-fertilization: The exchange of gametes between different individuals, which may or may not be related.

Outcrossing: A form of cross-fertilization, which specifies crossing between unrelated individuals.

Parthenogenesis: Any form of asexual reproduction through ova.

Recombination: Genetic exchange between homologous chromosomes during meiosis, especially when the exchange leads to gametes with allele combinations not represented on the parental chromosomes.

Self-fertilization: The fusion of gametes from the same individual.

Sex/rec: Shorthand for sexual reproduction and recombination.

Sexual reproduction: I use the term here to mean cross-fertilization between unrelated individuals. However, the term is more general and can be used to mean the incorporation of novel genetic material by any mechanism.

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